The Biological Systems Office

Annual Report

National Aeronautics and Space Administration
Office of Biological and Physical Research
Division of Physical Research

Performance Site
Johnson Space Center

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Contractors

Wyle Life Sciences
Universities Space Research Association
Futron Corporation

The contract may have as many as 100 employees depending on the project and flight schedules. Summary of contractor contributions to the Program is in Appendix 1.

Summary

The Cellular Biotechnology Program uses NASA cell culture technology and the microgravity of space to develop ground-breaking research in biomedical science. The Program emphasizes research in: 1) the engineering of tissue for research, transplantation, and biopharmaceutical production, 2) production of tissues for disease modeling such as cancer, 3) vaccine production through propagation of microorganisms, and 4) space cell biology as it relates to the transition of terrestrial life to low gravity environments and to the exploration of space. Our community of investigators extends throughout the country and includes august research organizations such as the NIH. The Program has produced technologies that introduce a new age to cell culture. These developments are patented, licensed, and commercially produced. The research and technological achievements are the basis for space act agreements, commercial ventures, and industrial partnerships. The outreach activities extend beyond science and into the community, undergraduate and graduate education, Congressional testimony, and a personal presentation to the President of the United States. Our future is rife with opportunity for applied science in ground-based applications and will extend into the use of living cells as reporter systems in sensors, the microencapsulation of drugs, and basic knowledge for human exploration and the search for life outside our planet.

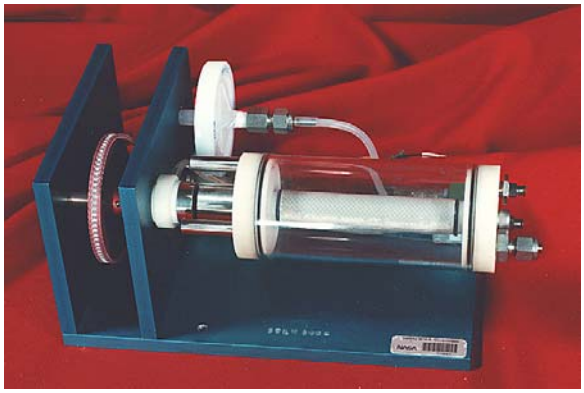
I. Introduction

The Cellular Biotechnology Program is managed by the Office of Biological and Physical Research in the Microgravity Physical Sciences Division of NASA. Having evolved from the Space Bioprocessing concepts of the 1970's, the purpose of the Program is **to use NASA technology and the microgravity of space to provide unique cell culture settings that address applied and fundamental cell science challenges.** In this context the Program addresses several goals:

1. *Develop ground-based and space bioreactors that serve the needs of the science community in the investigation of cell biology and tissue engineering.*
2. *Develop ground-based basic and applied science programs that use microgravity technology to investigate cellular processes.*
3. *Use the expertise and technology of NASA and its academic and commercial partners to advance tissue engineering to provide three dimensional, functional tissues for research, transplantation, and commercial applications.*
4. *Establish space cell biology as an academic discipline*
5. *Contribute to space exploration by providing technological advances in life support, health care, living exploratory probes, and space research.*

II. Technological Developments from the Program

The NASA Bioreactor



The flagship technological development of the Program is the NASA cell culture bioreactor. This bioreactor is the direct response to the science requirement for propagating human cells in a suspended state. In typical cell culture the cells sediment to the bottom surface of their container and propagate as a one-cell layer sheet. Prevention of such sedimentation affords the freedom for self-assembly and the propagation of three-dimensional tissue arrays. Suspension of cells is easily achievable using stirred technologies. Unfortunately, stirring invokes deleterious forces that disrupt cell aggregation and results in cell death. The NASA rotating bioreactor employs heretofore shunned strategies by completely filling the cylindrical culture vessel with fluid medium. Rotation on the horizontal axis results in the suspension of cells without stirring,

thus providing a suitable environment to propagate human cells without sedimentation to a surface.

The development of this bioreactor opened new vistas in tissue engineering, disease modeling, and space cell biology. It afforded an economical ground-based analog culture system and served as the conceptual basis for space cell culture bioreactors. The bioreactor is patented, licensed, and manufactured as the Rotating Cell Culture System (RCCS) by Synthecon, Inc. (Houston, TX). At this writing the manufacturer has sold nearly 5000 units.

The bioreactor has been further developed, patented and licensed through Wyle Life Sciences, to Celdyne Corp. (Houston, TX) in a different format that may afford unique cell culture advantages. The new Hydrodynamic Focusing Bioreactor (HFB), based on the principle of hydrodynamic focusing, was designed to enhance operations in space and to meet both operational and scientific requirements on orbit. The HFB simultaneously produces a low-shear fluid culture environment and a variable hydrofocusing force that can control the movement, location and removal of air bubbles from the bioreactor. The HFB is a rotating, dome-shaped cell culture vessel with a centrally located sampling port and an internal viscous spinner. The vessel and spinner can rotate at different speeds in either the same or opposite directions. Rotation of the vessel and viscous interaction at the spinner generate a hydrofocusing force. Adjusting the differential rotation rate between vessel and spinner controls the magnitude of the force.

The Hydrodynamic Focusing Bioreactor is an enabling technology for three-dimensional cell culture and tissue engineering investigations both in laboratories on Earth and on orbiting spacecraft. Use of this new bioreactor technology is expected to open new vistas in our understanding of basic cell function and three-dimensional tissue engineering as they relate to the basis of disease, tissue modeling and drug development. The use of the HFB to support three-dimensional cell culture and tissue engineering has widespread applications in tissue modeling and replacement. The HFB will support cell culture and tissue engineering investigations aboard the ISS in the Biotechnology Facility.

Sensors and Controls

The Sensor Laboratory was established in 1995 in response to requirements for pH, glucose, oxygen, and biomass sensors to operate process control systems in ground-based and space bioreactors. Such sensors will afford a physiologically balanced cell culture system and furthermore significantly decrease the resource demands in spaceflight-based cell culture. There is a two-pronged approach to acquiring the necessary sensors. A small effort is conducted in the Program laboratories and a greater effort is supported through the NRA awards.

pH Sensor

A non-invasive optical pH sensor was developed in our laboratory. The sensor was evaluated in perfused bioreactor cell culture experiments. The developed sensor performed satisfactorily in three cell-based experiments (two of 30-day and one of 124-day duration). During each cell-based evaluation, the pH sensor was calibrated only once. Furthermore, the sensor's performance was not compromised by the biofilm observed to have formed inside the walls of the internal cuvette.

The data was compiled in five in-house reports and was presented at the March 18-20,1999 IWG Meeting, titled "Continuous Monitoring of pH in a Rotating Wall Bioreactor using an Optical pH Sensor". A disclosure of Invention and New Technology was submitted June 1999. A paper is in press in the journal "Biotechnology and Bioengineering" titled "Continuous pH monitoring in a Perfused Bioreactor System using an Optical pH Sensor".

pH Control

A pH control system consisting of pH sensor, buffer, hardware and software was developed to control the pH of the culture media in the perfused bioreactor. The complete system was evaluated in perfused bioreactor cell culture, performing satisfactorily in three cell-based experiments (two of 30-day and one of 120-day duration).

The data was compiled in three in-house reports and was presented at the Sept. 6-8, 2000, SmartSystems 2000 conference, titled "An Automated pH Control Process in Mammalian Cell Culture in Perfused Bioreactors". A disclosure of Invention and New Technology was submitted in January 2002.

Glucose Sensor

An enzyme-based amperometric glucose sensor is being developed in our laboratory in collaboration with Dexcom, Inc.. The sensor was evaluated in a perfused bioreactor in three cell-based experiments (two of 30 day and one of 30+23 day). During 30+23 day cell run, two sensors were sequentially used. During this period, calibration was performed twice.

The preliminary results of the glucose sensor along with pH control experimental results were presented at the March 6-8, 2001 IWG meeting titled, "Performance of a pH control system and A Glucose Sensor in Perfused Rotating Wall Bioreactors". A paper detailing the developmental efforts and bioreactor cell run results was presented Sept. 2-7, 2001 at the International Electrochemical Society meeting, titled "On line Measurement of Glucose in a Rotating Wall Perfused Vessel Bioreactor using an Amperometric glucose sensor" and this paper is in press in the Journal of Electrochemical Society.

Oxygen Sensor

An optical oxygen sensor was developed in-house using the fluorescence quenching technique to measure the dissolved oxygen present in the perfused culture medium. The sensor measures dissolved oxygen non-invasively and the sensing system could be autoclaved for sterilization. The sensor was evaluated

in two 30 day bioreactor cell runs. During each cell run, a single calibration was used. Two in-house reports were submitted. Bioreactor cell run results were presented at the IWG meeting held at Palo Alto, CA during Feb. 26-28, 2002, titled "Performance of an Optical Oxygen Sensor in Perfused Rotating Wall Bioreactors."

Current Efforts

Several efforts are underway to benefit the future of microgravity research by developing technology that will continuously monitor and control the cell culture environment in bioreactors operation on-orbit. Sophisticated sensors are an important part of space exploration as well as in research on cell culture. These include Dr. David Murhammer and colleagues at the University of Iowa's investigation using near-infrared spectroscopy for real-time, non-invasive monitoring of selected parameters that are critical for animal cell cultures. Dr. Glenn Spaulding of the Clear Lake Medical Foundation, Inc. is working on optical sensors that monitor the cell culture media remotely. These physiological sensors are needed to achieve a physiologically balanced culture environment that will enable growth of tissues for transplantation. Also, Dr. Bruce Towe of the University of Arizona is working to develop a microflow oxygen sensor for space biotechnology.

Flight Hardware

Application Specific Preprogrammed Experiment Culture System (ASPEC)

The first in a series of bioreactor systems designed for growing cells in space. It is a self-contained cell growing and cell maintenance unit for use in spaceflight experiments. It consists of three units. Each unit consists of two major modules. The first one contains the power supply, the control computer and the avionics system. The second module has the cell growth chamber, the pump, the gas and the medium supply, life support sensors and sample storage container. Fluids are triple contained: the first level of containment is the culture chamber and the second level is the sealed aluminum box. The third level is the aluminum box outside the container box.

Bioreactor Demonstration System (BDS)

The objective of the Bioreactor Demonstration System (BDS) is to develop the capability and to demonstrate the ability to grow mammalian cells in microgravity. It is comprised of 4 different configurations: EDU, EDU-1, EDU-1R, and EDU-M.

Bioreactor Demonstration Unit (BDU)

The BDU is a rotating cylinder bioreactor that is supported by subsystems that provide media perfusion and exchange, continuous measurement and control of nutrient media, pH, glucose, oxygen, and carbon dioxide, incubator temperature control, and data storage.

Biotechnology Cell Science Stowage (BCSS)
This is the nomenclature for the support stowage that flies on the International Space Station. It consists of various soft stowed support items that are maintained at ambient, refrigerated, and cryogenic conditions. These items will be used to support cellular biotechnology experiments that occur on board the ISS.

Biotechnology Facility (BTF)
The BTF is a rack-level facility for the ISS to support experiments in cell science, protein crystallization, and separation science. This Biotechnology Facility is planned to hold up to seven biotechnology MLE payloads aboard ISS, and to provide power, gases, cooling, computers for payload operation and data archiving, video capture, and air and water purification. The BTF will include a Facility Control System to operate the BTF and interface with each of the individual experiment modules.

Biotechnology Oxygenator (BTO)
The Biotechnology Oxygenator is a fluid loop oxygenator. The development of this unit focuses on two requirements: first, the unit must be smaller and have less mass than the currently utilized unit; second, the unit must supply adequate oxygenation for cell culture over an extended period of time. The BTO is made from 15 feet of silicone tubing wrapped in two layers around a central core. Cell culture media flows through this tubing, which is encased in a sealed gas chamber. Gas flows through the chamber and diffuses through the silicone tubing to oxygenate the media.

Biotechnology Refrigerator (BTR)
The BTR is a Middeck Locker Equivalent sized, thermoelectric, temperature controlled unit. The BTR provides 0.57 cubic feet of refrigerated storage for temperature sensitive cell science supplies and samples being used in or transported to space.

Biotechnology Specimen Temperature Controller (BSTC)
The Biotechnology Specimen Temperature Controller is a Middeck Locker Replacement payload. It is a static bulk incubator bioreactor designed to maintain a homeostatic environment for cell growth. The BSTC is designed to support multiple cell culture experiments simultaneously. Multiple cell lines are grown within individual Teflon bags called Tissue Culture Modules (TCM). Compared to the rotating vessel bioreactors, the BSTC typically grows cultures for a limited time (~14 days). It does, however, provide the advantage of allowing multiple experiment or replicate experiment cell growth whereas the rotating experiments typically involve one culture per experiment run.

Biotechnology System (BTS)
The BTS provides the resources and hardware that, in combination, provide an environment suitable for sustained cell growth. In addition, the BTS was

designed to mount and operate in different space vehicles that were required during various phases of the experiment. To keep the biologically active materials within the prescribed thermal and cultural conditions, the BTS was designed to remain operational during the pre-launch, launch, ascent, on-orbit, and descent phases of the mission.

Biotechnology Water Treatment System (BWTS)
The BWTS treats, processes and filters contaminants from ordinary Shuttle Galley water. The result is ultra-pure water that is suitable for use in cell culture experiments. The BWTS could eventually replace the need to manifest separate supplies of ultra-pure water on the Shuttle and the International Space Station. Water purification is achieved through a combination of activated carbon, a mixed-bed ion exchange resin and microbial filters. On STS-111, the BWTS was tested and produced water suitable for cell cultures.

Cell Radiation Experiment System (CRES)
CRES is a perfused cell culture system for maintaining cells in a homeostatic environment, irradiating the cells through a thin polymer window and monitoring the effects of radiation and radiation repair in those cells. It may be used to predict the efficacy of various anti-tumor treatments such as (1) drug treatments (2) radiation treatments, (3) combined drug and radiation treatments. The effects of these treatments can be studied on normal cells and tumor cells. CRES can also be used to analyze the influence of radiosensitive or radioprotectant drugs on cells subjected to radiation. This knowledge will play a role in protecting astronauts, medical equipment operators, and nuclear power plant workers. However, it's most immediate impart will be as a means for customizing anti-tumor chemo- and radiation therapies for cancer patients.

Cellular Biotechnology Cryodewar (CBC)
0.5 Middeck Locker Equivalent long duration cryodewar that utilizes Liquid Nitrogen to cool cell inoculums prior to experiment initiation on-orbit.

Cellular Biotechnology Operational Support System (CBOSS)
Nomenclature for the manifested Cellular Biotechnology compliment of payloads that support operations on the International Space Station. Current configuration includes the use of BCSS, BSTC, BTR, and GSM.

Centrifugal Adsorption Cartridge System (CACS)
CACS is an apparatus that recovers one or more bioproducts from a dilute aqueous solution or suspension flowing from bioreactor. The medium flows through the absorbent in a spiral fashion along a specially designed ramp. The centrifugal effect of the flow forces bubbles radially inward toward and through the gas-permeable, hydrophobic inner membrane. As the medium flows through the absorbent, targeted molecules (bioproducts) are a selectively captured by the absorbent and are removed from the medium. The CACS can be used both in the unit gravity environment of earth and in low-gravity environment of space. It

can either be connected downstream from the bioreactor or into a flow loop that includes the bioreactor so that the liquid can be recycled.

Data Acquisition and Control System (DACS)
The DACS is hardware, firmware, and software system designed to monitor, operate and control experiment-specific systems and facility-based systems in the BTF. Hardware includes an experiment control Computer (ECC), power module, and PCMCIA data storage cards. Firmware involves the software "embedded" in the ROM on the CPU. The additional software is the MS-DOS and RT Kernel system files as well as program files for monitoring and controlling the experiment and/or facility system. Many of the components will be developed using commercial-off-the-shelf (COTS) applications.

Detailed Supplementary Objective (DSO 316)
This is the first flight hardware developed and flown by the Biotechnology group. The unit was designed to photograph spheres suspended in a PBS (Phosphate Buffered Saline) solution. The hardware consisted of a 500 ml perfused vessel and plumbing, video camera and control computer. Once on orbit and activated, the computer ran through a series of preprogrammed steps altering the vessels rotational and perfusion rate parameters. The video camera recorded the movement of the particles within the vessel. The videotapes of the vessel and particles obtained during this experiment were returned and analyzed for particle trajectory.

Detailed Supplementary Objective (DSO 322)
DSO 322 is an apparatus containing four independently controlled incubator/refrigerator modules. Each module can house one chamber slide containing up to 8 wells. The unit is normally programmed to refrigerate all four modules during ascent. Once on orbit a crew member can command the unit to run a profile which turns the heaters/refrigerators on or off independently at predetermined times.

Detailed Supplementary Objective (DSO 316A)
This apparatus was used to study the flow fields within a perfused non-rotating bioreactor chamber. The unit consisted of a control computer, video camera and chamber with the required pumps, valves and plumbing. Once on orbit and activated the unit would run through a series of predefined steps which varied the pump rate, flow direction and pumping duration while videotaping dye within the chamber. After return to Earth the tapes were analyzed for flow patterns.

Engineering Developing Unit-1 (EDU-1)
The EDU-1 contains a perfused rotating cell-culture vessel and subsystems to provide infusion and perfusion of culture medium to control the oxygen and carbon dioxide levels within the experiment, temperature control to maintain incubator module at 36±0°C, and the software required to monitor and control the experiment.

Engineering Developing Unit-1 Reflight (EDU-1R)
The EDU-1R is a bioreactor system used to grow three-dimensional tissue cultures in space or in simulated microgravity on earth. The EDU-1R houses a rotating wall perfused vessel that is maintained at 36 degrees C. The vessel will support cell growth for an experiment period of up to 20 days. During this term, the system maintains temperature, circulates and oxygenates media, and facilitates removal of media samples, cell samples, and expended products.

Automated Rotating Culture System (ARCS)
The ARCS is a Middeck locker equivalent sized payload currently being developed for NASA's Cellular Biotechnology Office. The ARCS payload will be designed to support the growth and development of three-dimensional tissue cultures, facilitate the removal of cell and tissue samples during the experiment, and monitor culture health during experiments on board the Space Shuttle and the International Space Station.

Engineering Development Unit-Mir (EDU-M)
The EDU-M is a modification of the configuration of the EDU-1 flown on Mir. It houses a rotating wall perfused vessel in a controlled atmosphere held at 36±1°Celsius with support system and electronics for data logging and post flight analysis of system performance. The bioreactor vessel volume of 125 ml contains fluid growth medium and will be oxygenated as needed to support the cell growth. The front panel has 3 accessible connectors: Power, Analog and Digital. It also contains a Power circuit breaker and switches for disabling /enabling the gas, disabling/enabling the G-sensor and starting/stopping vessel rotation. There is a button to turn on the internal light (for video taping), and inlet, outlet and exchange ports to enable sampling, waste removal and media infusion. There is a view port, a camera attachment and an experiment mode indicator.

Engineering Development Unit-Mir Reflight (EDU-MR)
Modification of configuration EDU-M

Experiment Control Computer (ECC)
The ECC provides the computer control resources required for automated, long-duration cell science and tissue engineering investigations on orbit.

Experiment Control System (ISS unit) (ECS)
The ECS is used to independently control each cell culture and tissue engineering experiment module.

Gas Supply Module (GSM)
The GSM is a half middeck locker equivalent payload that provides a blend of oxygen, nitrogen, and carbon dioxide to experiments at a delivery pressure of 40

psig. The pre-mixed gas is provided through external hoses that connect the front panel of the GSM to a bioreactor or an incubator.

Glucose Sensor (Glucose Sensor)
This sensor measures the concentration of glucose present in culture media. The sensors key component is a membrane that has been impregnated with a glucose oxidase enzyme. The glucose in the culture media reacts with the glucose oxidase enzyme and oxygen to produce hydrogen peroxide. The electrical current created by this reaction is then measured using a standard electromechanical anodic oxidation process. The sensor can measure glucose concentration in a range between 20 and 250 mg/dl ± 15 mg/dl

Hydrodynamic Focusing Bioreactor (HFB)
The HFB is a rotating wall bioreactor that provides a unique hydrofocusing capability that simultaneously enables a low-shear culture environment and a unique hydrofocusing-based "herding" of suspended cells, cell aggregates and air bubbles. The HFB is a rotating dome-shaped cell culture vessel with a centrally located sampling port and an internal rotating viscous spinner attached to a rotating base. The vessel and viscous spinner can rotate at different speeds and in either the same or different directions. Adjusting the differential rotation rate between the vessel and spinner, results in a controllable hydrodynamic focusing force. The resultant hydrodynamic force suspends the cells in a low shear fluid environment that supports the formation of delicate three-dimensional tissue assemblies. The three versions of the HFB vessels include the HFB-S flight unit and the HFB-40 and HFB-160 ground units.

Microencapsulation Electrostatic Processing System (MEPS)
The Microencapsulation Electrostatic Processing System is a flight hardware system designed to form multi-layered, liquid-filled, microcapsules containing pharmaceuticals. The MEPS automated operations bring together two immiscible liquids with low shear fluid jetting along the fluid interface. The liquid-filled microcapsules are surrounded by a thin, semi-permeable outer membrane that is permeable to the drug molecules contained within. The MEPS makes drug filled microcapsules, then filters them, washes them, and in some experiments, the microcapsules are re-suspended in a special coating solution, then a high voltage electrostatic field is applied to the suspension which causes the coating material to rapidly deposit on the outer surfaces. The coatings of microcapsules are designed to alter their surface charge which makes them less recognizable by immune cells in the blood stream. After coating they are harvested by pumping into a separate reservoir for storage until return to earth. An average MEPS experiment takes about two hours, and a built-in-video-microscope monitors and records critical stages of the process. Each experiment is housed in a separate Process Chamber Module (PCM) that contains all fluids, reservoirs, motors, valves and sensors. The first PCM is pre-installed in the MEPS and after each experiment run the MEPS is powered down and PCM is removed, stowed, and replaced by the next PCM.

Oxygen Sensor
A fluorescence based oxygen sensor that measures the dissolved oxygen (DO) present in the perfused media in a bioreactor. The fluorescence obtained, while exciting a Ruthenium (II) complex with a blue light quantitatively quenches the DO present in the media. The amount of fluorescent light is correlated to the concentration of oxygen present in the media.

Perfused Stationary Culture System (PSCS)
The Perfused Stationary Culture System (PSCS) is designed as a small volume, multi-vessel system to support on-orbit cell culture and tissue engineering investigations on-orbit. Small volume vessels will enable multiple experiments to be conducted during a single flight increment using small volumes or amounts of biological material. The PSCS culture vessels can be inoculated on the ground or on-orbit, and can be removed and replaced on-orbit.

pH Sensor
The pH sensor is a noninvasive optical sensor that monitors the pH of the perfused culture media in a bioreactor. The optical absorption changes of phenol red in culture media due to pH changes are monitored and correlated to the pH of the media. The pH sensor can measure the pH of the culture media within + 0.1 pH unit in the pH range between 6.5 and 7.4.

Rotating Wall Perfused System (RWPS)
The RWPS is a bioreactor system used to grow three-dimensional tissue cultures in space or in simulated microgravity on earth. The EDU-1R houses a rotating wall perfused vessel that is maintained at 36 degrees C and supports long-term cell growth up to 120 days. During this term, the system maintains temperature, circulates and oxygenates media, and facilitates removal of media samples, cell samples, and expended products.

Rotating Wall Perfused Vessel (RWPV)
The RWPV is a bioreactor system that overcomes gravity-induced limitations and creates a low-shear culture environment that enables technologies for three-dimensional cell culture and tissue engineering in microgravity.

Microencapsulation Technology

Microgravity offers novel advantages in work with multiphase fluid systems. Recent research has led to the development of a new method of making liquid-filled microcapsules as a unique drug delivery system. These new microcapsules contain anti-tumor drugs, a radio-contrast medium (which allows the distribution of the capsules to be imaged with C-T scanning), and a magnetic

trigger particle (which allows the microcapsule to be lysed open when a harmless magnetic field is applied from outside the body). The new Microencapsulation Electrostatic Processing System (MEPS) was flown and tested on STS-95 by Senator John Glenn, NASDA astronaut Dr. Chiaki Mukai, and ESA astronaut Pedro Duque. The MEPS experiments on STS-95 successfully made microcapsules containing three different types of anti-tumor drugs.

For the first time microcapsules were formed, rinsed, then coated with a thin layer of another polymer (using an electrostatic field) which changes the electrical charge on the surface of the microcapsules. This is important for targeting to specific tissues and avoiding attack by immune cells.

Microcapsules have been made for chemoembolization of vascular tumors, wherein the microcapsules are injected into an artery leading into the tumor. However, they are too large to pass through the tiny arterioles, therefore, they form emboli blocking the blood flow within the tumor, and the anti-tumor drug slowly leaks out directly into the tumor tissues.

Microcapsules containing very dense radiocontrast medium have been used to enhance C-T scanning of small vascular systems in deep seated organs. The utility of this NASA Microcapsule technology has been demonstrated in animals by studies at the Texas A&M College of Veterinary medicine.

Microcapsules have been made which contain a small ceramic/magnetic bead. After the microcapsules are injected into the target tissue, the drug can be released days later, by having the patient exposed briefly to a magnetic field normally used for diagnostic imaging (MRI). The magnetic field heats the beads until they become warm enough to melt a hole in the microcapsule, rapidly releasing the drug within. The magnetic field is not strong enough to either harm the patient or cause side effects. Applications include timed release of growth factors to promote healing and tissue re-growth weeks after surgery.

This system has been used on ten space flights since 1991. Experiments using modified commercial flight hardware have been conducted on the Microencapsulation Electrostatic Processing System (MEPS) - six experiments have been successfully conducted on STS-95.

Six U.S. Patents have been filed, three have issued, one approved, and two are pending. There have also been three additional NASA Patent Disclosures.

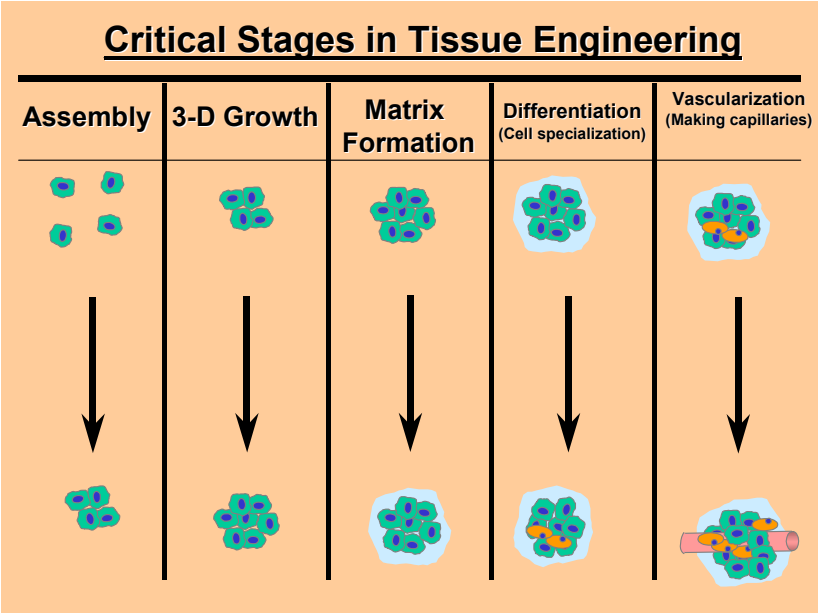
Seven papers in U.S. and International Journals, nine abstracts of presentations at National & International Science Meetings, and two book chapters have been published. Presentations were given at Technology 2002 and Technology 2003.

III. Ground-Based Science Programs

The development of the bioreactor resulted in the emergence of a new research format for NASA and provided new options for cellular investigations in the science community. As the bioreactors became available, the number of investigators in the NASA sponsored program grew from approximately 10 in 1993 to more than 100 in 2000. There are more scientists *outside* of the NASA sponsorship umbrella using the bioreactor than within the Program.

The ground-based science program spawned research in many aspects of cell biology and space science. The flagship effort was in tissue engineering wherein the microgravity of space may afford a unique advantage in the propagation of human tissue starting with individual cells. The NASA bioreactor was used to profile the strategy on the ground since it models microgravity by maintaining cells in continuous fall and randomizes the gravity through the cell. The engineering of functional tissue is a complex process that requires many different events to occur in a specific order. The Program targeted five major milestones in tissue engineering to pursue as an index of feasibility:

1) Three dimensional freedom of assembly without sedimentation to a planar surface



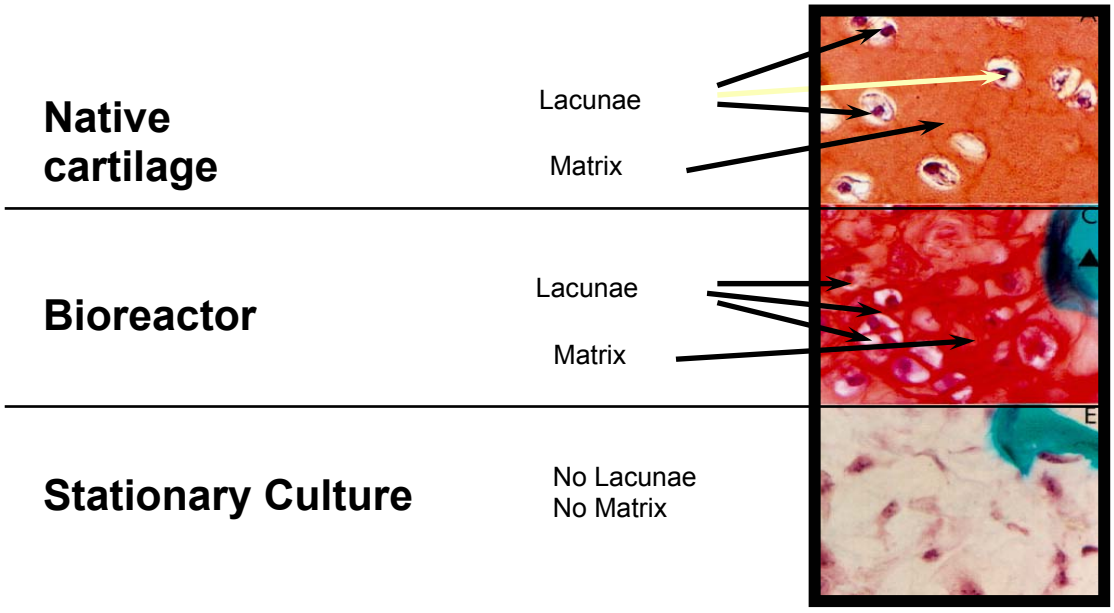
2) Three-dimensional growth of cell assemblies
3) Synthesis and elaboration of native matrix to strengthen and stabilize the tissue
4) Differentiation of cells to conduct specialized functions within the tissue
5) Development of artificial or natural capillaries for delivery of nutrients and dissipation of waste.

The NASA bioreactor can propagate mammalian tissue up to approximately 0.5 inches in diameter, the upper limit in mass that can be supported in a rotating body of fluid on the ground. Larger assemblies require microgravity where the mass limitation is relieved and replaced by accessibility of

nutrients. The following descriptions will chronicle the research that demonstrates that the first four milestones have been achieved.

Tissue engineering research established the bioreactor as a powerful technology in cell culture. Initial experiments performed by Dr. Lisa Freed and by Dr. J. M. Jessup readily demonstrated the contribution of the bioreactor to tissue engineering. The experiments by Dr. Freed showed that small constructs of cartilage can be produced from individual cells using the bioreactor. These constructs bore many of the characteristics of native cartilage. Currently, the investigator is using this approach to produce cartilage for transplantation in animal models.

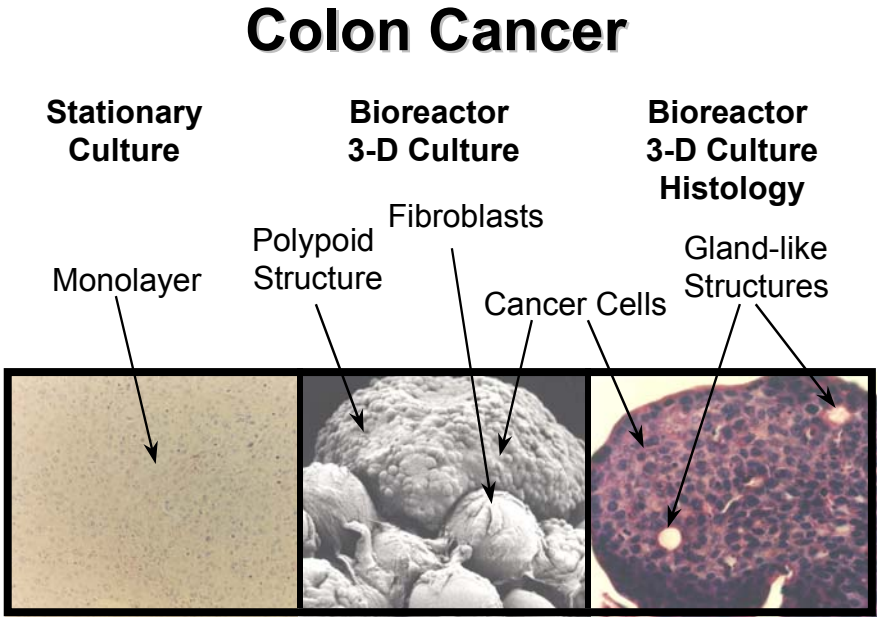
Cartilage Development in the NASA Bioreactor



The ability to engineer tissues opens new possibilities for disease-related research. Dr. Jessup used the bioreactor to model human colon cancer. The results showed that the cancerous tissue formed in the bioreactor displayed remarkable similarity to that obtained at biopsy. The model affords a new approach in cancer research that enables insight into the complex dynamics between normal and cancerous tissue and how that relationship contributes to tumor progression and metastasis.

The Program supports investigations of the major cancers and in other diseases. These include investigations targeting prostate, ovarian, breast and endocrine tumors. Additionally, the bioreactor is used to model endometriosis and to

mature pancreatic islet cells for the production of insulin. In summary, the following tissues have been propagated in the NASA bioreactor: cartilage, liver for hepatitis pathogenicity model, human kidney, liver for extracorporeal support, lymphoid tissue for HIV pathogenesis, thyroid, skin, pancreatic islet cells, neuroendocrine cells, intestinal epithelium for Norwalk Virus production for vaccines, and cardiac and skeletal muscle. Some are illustrated below. (See Appendix 4)



Propagation of functional human liver for experimental, medical and commercial needs has been sought for several decades. At best, differentiated tissue can be maintained for 16 days by conventional culture methods. Dr. Boris Yoffe and colleagues used the NASA bioreactor to produce functional liver constructs that are viable in excess of thirty days. These findings are in part the basis for a major commercial venture that will seek to use our technology for high throughput analysis of drug metabolism and breakdown products and for development of an extracorporeal liver support device to maintain patients in liver failure while awaiting transplantation. The Space Act Agreement and proposal by Fisk Ventures and StelSys, Inc. will directly address the utility of bioreactor technology and space microgravity in the development of commercial and medical applications of liver tissue.

The bioreactor serves as an analog for space cell biology. . Originally it was theorized that cells are too insignificant in mass to be affected by a reductionsin gravity. The findings from bioreactor research are compelling and suggest that there is much to discover from cells in microgravity. Testinghypotheses in the bioreactor has led to more mature space experiments and increased the scientific output from space missions.. Cells respond to the analog microgravity conditions by of bioreactors by: decreasing their surface area to volume ratio, decreasing the quantity of signals traveling across the cell membrane, decreasing their locomotor activity, differentiating, changing their gene expression dramatically, changing their rates of secretion and metabolism, reorienting organelles, and many other ways

Locomotion of Human Immune Cells

A normal function of lymphocytes, immune cells, is to move through the matrix between cells. Analysis of human immune cells that have been in the analog culture system reveals a near total loss of locomotory function. This observation has been confirmed in two flight experiments. The significance of these findings extends into our understanding of the potential effects of microgravity on immunity, particularly in long exploratory missions. Secondly, it may have compelling effects on other processes that rely on cell movement, i.e. embryogenesis (fetal development). Knowledge of this defect establishes targets for countermeasures.

Differentiation

The process by which cells develop a specialized function within a tissue is differentiation. Research in the bioreactor is offering insight into the gravity-induced changes in differentiation. Dr. Timothy Hammond has shown that kidney cells grown in the bioreactor differentiate and mature to function more like the cells in the organ. His research is significant in that this is the first venue to induce a stable differentiated state in the kidney cells, to demonstrate the synthesis of critical biomolecules (precursors of Vitamin D), and to display structures indicative of mature tubule cells of the kidney. These observations are the basis for a commercial development that will use both bioreactor technology and microgravity. A similar development is occurring with the propagation of differentiated liver by Dr. Boris Yoffe. His work will result in tissues to be used for investigating the pathogenesis of hepatitis viruses. Dr. Wei-Shou Hu and colleagues are developing a bioartificial liver and investigating manufacturing tissue-like liver cells in the bioreactor for use in clinical investigations.

Gene Expression

Adaptation to a new environment is attended by a change in the suite of genes that the cell will turn on and turn off. Gravity changes, as with other physical stimuli, result in changes in gene expression. Knowledge of the gene

expression in analog culture and microgravity afford critical insight into the consequences of microgravity on cell function, bacterial and fungal populations, and exploration processes. The first profile of gene expression in the bioreactor and in space was conducted by Dr. Timothy Hammond (*vide infra*).

Signal Transduction

Cells respond to their environment through receptors on their surface. The receptors are stimulated by hormones, growth factors, toxins, etc. Once stimulated the receptor transduces the signal to the inside of the cell. Thereafter the cell will conduct a series of responses that favor adaptation to the new environment. The process of signal transduction is affected by microgravity. Therefore the beneficial, as well as deleterious effects observed in microgravity, no doubt are due in part to the changes in signal transduction. A significant number of our investigators are seeking to identify the lesions in signal transduction and to determine the mechanism by which the physical change (diminution of gravity) translates into altered cellular biochemistry. This research is important to the understanding of basic cell biology processes the application of microgravity and bioreactor technology to tissue morphogenesis, as well as the elucidation of the critical factors in the transition of terrestrial-based life to low gravity environments.

The Program sponsors a panel of investigations in signal transduction. Dr. Arthur Sytkowski investigates the response of red blood cell progenitors to the hormone erythropoietin in modeled microgravity. Dr. Peter Lelkes investigates the response on neuroendocrines cells. The latter has conducted flight investigations.

Propagation of Cells that Host Infection

There are numerous agents of infectious disease that are resistant to propagation in culture or do not express virulence factors when cultured. Many of these bacteria, viruses, and protozoa require living cells as hosts for growth in culture. Recently, viruses, bacteria, and protozoa have been propagated in the bioreactor. Propagation of an organism not only is essential to understanding infectious processes, but it is also, key to the development of vaccines and antibiotics. Agreements with venture groups and with drug companies (Wyeth-Lederle Laboratories and Viragen, Inc.) will include use of this strategy for development and commercial production.

NRA Funded Research

The NASA/NIH 3-D Tissue Laboratory

The NASA/NIH 3-D tissue culture laboratory was initiated in 1994 in the National Institute of Child Health and Human Development (NICCHD) in the

laboratories of Dr. Joshua Zimmerberg. The collaboration established a multidisciplinary deployment of NASA cell culture technology for use in investigating basic principles in cell and molecular biology. The applications are extensive and include many other institutes of the NIH and therefore outlined below.

1. National Institute of Child Health and Human Development
    A. HIV infection in human lymphoid tissue in RWV bioreactor
    B. The effect of microgravity on the immune function of human lymphoid tissue
    C. Development of an advanced dual-photon microscope for 3-D tissue analysis
    D. Use of RWV bioreactor to culture endometrium biopsies
    E. Culture of Hermanski-Pudlak Syndrome fibroblasts
2. National Cancer Institute
    A. Long term maintenance of human prostate tissue in the RWV bioreactor.
    B. Study of Lyme disease in RWV bioreactor
3. National Institute of Diabetes and Digestive and Kidney Diseases
    A. Culturing esophageal carcinoma cells in RWV bioreactor
    B. Culturing human islet cells in the RWV bioreactor
    C. Use of RWV bioreactor for whole mouse embryo culture
4. National Institute of Dental Research
    Differentiation of salivary gland cells in the RWV bioreactor
5. National Institute of Arthritis and Musculoskeletal and Skin Diseases
    Culture of synovial tissue from rheumatoid arthritis patients
6. Other Federal Agencies and collaborators of the NASA/NIH 3-D Tissue Culture Lab.
    Food and Drug Administration
        Replication of human intestinal parasite in intestinal cells in the RWV bioreactor
    Naval Medical Institute
        RWV bioreactor models of human squamous metaplasia in the lung
    United States Army Medical Research Institute for Infectious Diseases
        Assessment of the RWV as a “Universal” pathogen culture system
    Johns Hopkins University
        Cryptosporidium infection of intestinal tissues and cells
        Institut Cochin de Genetique Moleculaire, Paris, France (in collaboration with LCMB, NICHD)
        Study of HIV mucosal transmission

IV. Flight Experiments

The Program has proven productivity in shuttle flight experiments and operations. Our brief history has afforded relatively few flight experiment opportunities (STS 111/ ISS UF2, STS-108/ISS UF-1, STS-107, STS-105 / ISS 7A-1, STS-106, STS-95, STS-90, STS-85, STS-70, STS-67, STS-62, STS-57, STS-56, STS-54, STS-44). We conducted three long duration risk mitigation experiments on Mir (Mir Increment 7, STS 86-89/Mir 6, STS 79-81/Mir 3). The Mir experience facilitated the development of long duration operation cell culture hardware, profiled a facility level operation of a hardware complement, and gave exciting insight as to the potential for research output from an orbiting laboratory facility. The experiments are summarized below and are followed by the publications resulting from the flight experiments.

A. Documentation of Operation of the Space Bioreactor (STS-44).

Development of rotating bioreactors for use in microgravity required proof of operation principles on orbit. This flight experiment clearly demonstrated the modeled concepts and paved the way for the development of the perfused flight bioreactors.

Fluid Dynamics Within a Rotating Bioreactor in Space and Earth Environments. *Journal of Spacecraft and Rockets* 31:6 937-43, Dec. 1994. Tsao, D.Y., D.A. Wolf, G. Spaulding, and E. Boyd.

B. Impaired locomotion of lymphocytes in space STS-54,-56.

The ability of human immune cells to invade the matrix between cells is a critical function in protection against infection. The flight experiment confirmed the observations in the ground-based bioreactor and initiated the use of the bioreactor as a microgravity analog culture system. The results clearly documented an impairment of locomotory function. It was the first report indicating a potential impairment in cellular movement in microgravity.

Changes in gravity inhibit lymphocyte locomotion through type I collagen. *In Vitro Cellular & Dev. Biol. Anim.,* 33(5):398-405, May 1997. Pellis, N.R., T.J. Goodwin, D. Risin, B.W. McIntyre, R.P. Pizzini, D. Cooper, T.L. Baker, and G.F. Spaulding.

C. Application-Specific Preprogrammed Experiment Culture (ASPEC) (STS-57)

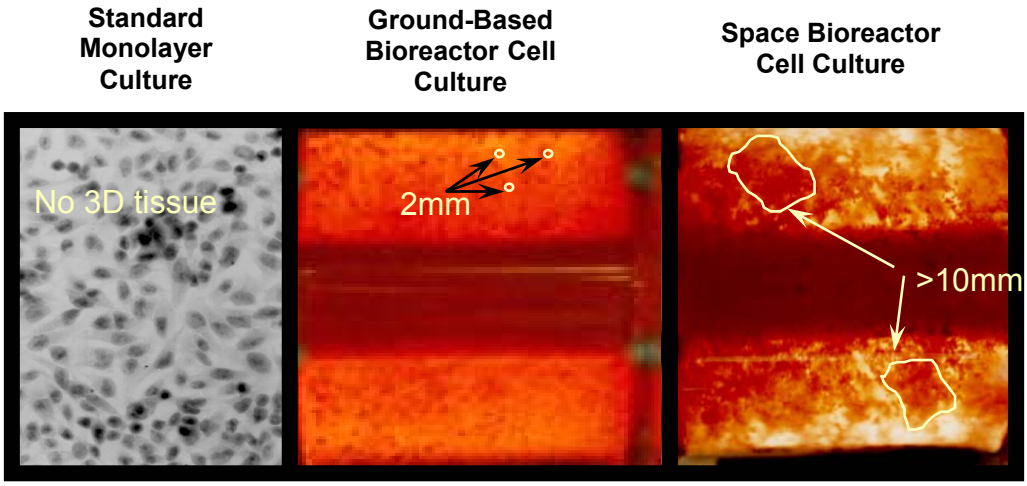
The Application-Specific Preprogrammed Experimental Culture was an experiment that focused on verifying engineering designs and procedures for a complex integrated three-dimensional cell culture system. It was a significant step in developing tissue-culture capability technology in space and in the ground.

D. Growth of mammalian cells in unfacilitated mass transfer (STS-62)

The development of incubators and space bioreactors required practical knowledge of the mass transfer environment within the culture vessel. STS-62 was an incubator experiment that demonstrated small volumes of medium experienced sufficient disturbance to provide small populations of cell with nutrients. The experiment bolstered confidence for the efficacy of a differentially-rotated concentric cylinder format to provide the cells with adequate mass transfer.

E. Demonstration of the unique contribution of microgravity to cell aggregation and assembly (STS-70,-85)

As illustrated previously, assembly of cells without sedimentation to a surface is an important milestone in the demonstration of microgravity as a tool in tissue engineering. The experiment conducted by Dr. J.M. Jessup used human colon cancer cells to determine the impacts of microgravity on the cell culture and the relationship of observations in the ground-based bioreactor to those in space. Results showed superior assembly, indicators of differentiation, and unique metabolic changes in space.



Microgravity Culture Reduces Apoptosis and Increases the Differentiation of a Human Colorectal Carcinoma Cell Line. *In Vitro Cellular and Dev. Biol*. Anim. 36(6): 367-73, June 2000. Jessup, J. M., M. Frantz, E. Sonmez-Alpan, J. Locker, K. Skena, H. Waller, P. Battle, A. Nachman, Bhatti, M. W. Weber, D. A. Thomas, R. L. Curbeam, T. L. Baker, and T.J. Goodwin.

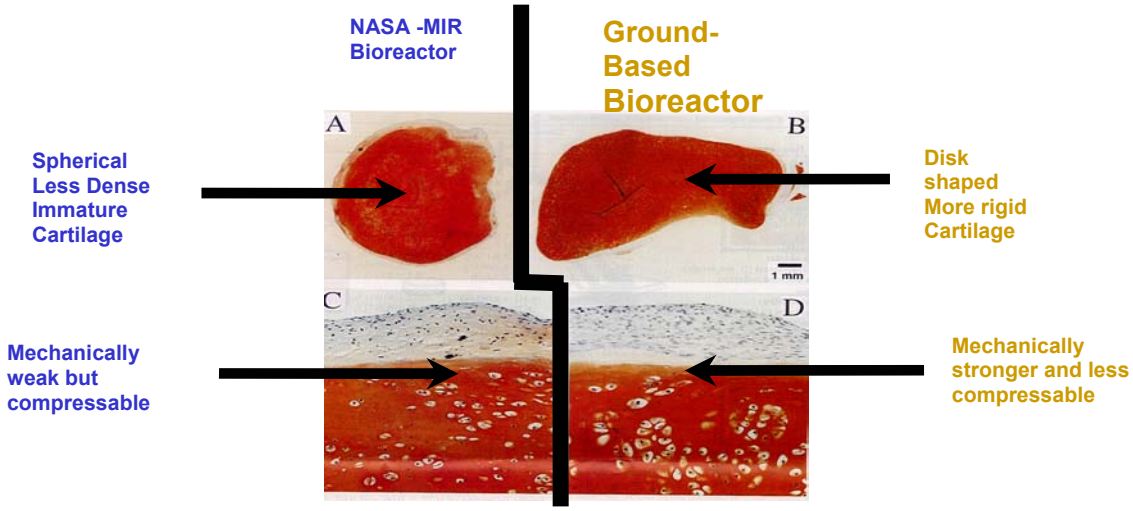
F. Assessment of the life and function of silicon-based data storage on Mir. Development of the maintenance and repair software to use non-mechanical 'hard drive' storage (Mir Increments 2,3, and 5)

Experiments conducted in earth orbit must accommodate numerous variables to understand the relative contributions of microgravity, radiation, and acceleration on biological systems and on the operation of cell culture support equipment. The susceptibility of silicon-based data storage to corruption was

investigated in a long series of tests and experiments. Results showed that the exposure of silicon-based storage to radiation on the Mir space station resulted in single event upsets in powered storage cards and that unpowered cards were more resistant. Furthermore, a sentinel program was designed to repair upsets in real time. The concept was demonstrated on orbit. The entire investigation is detailed in an internal NASA report.

G. Use of microgravity to propagate large cartilage constructs (STS-79 Mir Increment 3).

Engineering of functional tissue may require extended durations of cell culture. Cartilage tissue was chosen as an early candidate because of the low metabolic demand, durability, and convenient markers of maturity. The opportunity to develop and test long term operating cell culture hardware was consistent with the strategy for use on Mir. The experiment established several landmarks. First, it was the longest duration continuous cell culture in space (137 days). Second, it clearly demonstrated the unique advantages of tissue engineering in space. Third, it showed the differences in tissue morphogenesis in space versus the ground-based bioreactor.



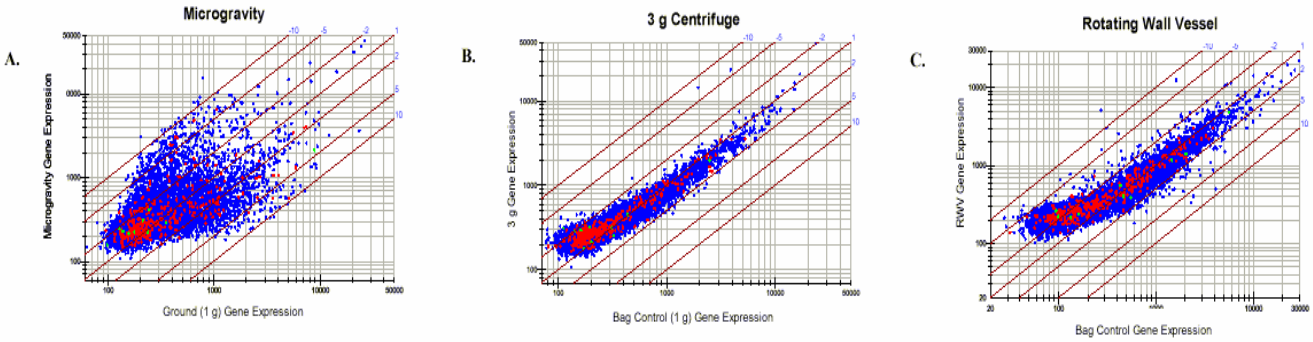
Tissue Engineering of Cartilage in Space, *Proc. Natl. Acad. Sci*. 94 (25)pp. 13885-13890 Dec. 1997. Freed, L.E., Robert Langer, I. Martin, N. Pellis, and G. Vunjak-Novakovic.

H. Human renal tubular cells (STS – 90)

This research investigated the mechanisms of differentiation of rat renal cells growing in the BSTC as the microgravity culture system. The engineering performance of the BSTC as flight hardware to support cell culture was validated and components were identified which required refurbishing.

I. Mapping the genetic signatures of cells in space (STS-106)

A series of experiments in space incubators using several different cell populations revealed critical findings for future experiments in tissue engineering and for space cell biology. A group of investigators conducted experiments for post flight analysis. The isolated kidney and neuroendocrine cells revealed microgravity unique responses. Below are the results of the gene expression analysis in kidney cells. Each of the dots represents the magnitude of the gene expression change relative to the ground-based control. If there were no changes in any of the 10,000 genes tested, all the dots would line up on the diagonal line. The first panel shows that expression changes in microgravity are dramatic. More than 1600 of the 10,000 genes change expression when cells are transferred to microgravity. In contrast (center panel), only 70 are changed by hypergravity. Finally about 800 are changed in the ground-based bioreactor. Of that 800 about 200 are shared with the microgravity array. The significance of these experiments reaches far beyond tissue engineering. This is the first definitive analysis of the adaptation response of human cells to microgravity. It is also an important aspect of the research sought by a commercial investment group. Thus Dr. Hammond and Tulane University are part of the consortium formed by Fisk Ventures.



Mechanical Culture Conditions Effect Gene Expression: Gravity Induced Changes on the Space Shuttle *Physiological Genomics* 3 (3):163-173, 2000. TG Hammond, E. Bennes, KC O'Reilly, DA Wolf, RM Linnehan, A. Taher, JH Kaysen, P. L. Allen, TJ Goodwin.

Gene Expression in Space. *Nature Medicine*. 5 (4):359. April 1999 Hammond, T.G., F.C. Lewis, T.J. Goodwin, R.M. Linnehan, D.A. Wolf, K.P.Hire, W.C. Campbell, E. Benes, K.C. O'Reilly, R.K. Globus, and J.H. Kaysen.

Growing Tissues in Microgravity. *Nature Medicine*, (8):901-7 August 1998, B. R. Unsworth and P. I. Lelkes.

J. Evaluation of ovarian tumor cell growth and gene expression (STS-105 / 7A.1)

This investigation set out to characterize complex three-dimensional development of the LN1 ovarian tumor cell line and thus provided important insight into structure-function relationship as these cells assemble into tissue-like masses. The ovarian tumor cell protocol will characterize complex three-dimensional development of the LN1 human ovarian tumor cell line, thus providing important insight into structure-function relationships as these cells assemble into tissue-kike masses. The growth and differentiation of these stem cell-like cells will be examined in order to characterize morphological changes occurring during three-dimensional growth in conjunction with determination of accompanying alterations in cell cycle kinetics, cell cycle proteins and cellular oncoproteins. The resultant information will be applied towards defining potential points of cellular development which may be targeted for treatment in patients with this disease

K. Use of NASA Bioreactor to study Cell Cycle Regulation Mechanisms of Colon Carcinoma Metastasis in Microgravity (STS-105 / 7A.1)

Dr. Jessup is a veteran of two space flight experiments on STS70 and STS85. His work from these flights has resulted in two peer reviewed publications in national journals regarding metastatic characteristics of colon carcinoma. In order to gain additional needed information regarding the mechanisms involved in this disease additional flight experiments are necessary.

L. PC-12 pheochromocytoma cells: A proven model system for optimizing 3-D cell culture biotechnology in space (STS-105 / 7A.1)

In this experiment the ability and extent of the differentiation in actual microgravity will be assessed by growth and subculture of PC-12 cells in the BSTC. Neuroendoctine cells (PC-12) are known to produce biologically active modules called catecholamines, important to normal function and pain suppression as they differentiate. Precursors to these molecules are Dopamine Beta Hydroxylase (DBH) and Phenylethanolamine Methyl trasferase (PNMT). Evidence of this differentiation is seen on ground-based simulated microgravity rotating wall systems. The ability and extent of differentiation in actual microgravity will be assessed by growth and subculture of these cells in the BSTC on Mir.

M. Renal cell differentiation and hormone production from human renal cortical cells (STS-105 / 7A.1)

On Space shuttle mission STS-90 human renal cortical cells were flown and genetic analysis performed after return to Earth. As a consequence significant data was uncovered regarding the molecular genetic expression of human cells in microgravity and their ability to be manipulated to produce valuable renal hormones. Continued studies in microgravity are expected to reveal additional information regarding the mechanisms involved in these genetic manipulations

and responses. Goals of these experiments will be to again create three-dimensional growth of normal human renal cells, assess the production of erythropoietin and vitamin D3 and assess the model for production of commercial applications.

N. Evaluation of induced erythropoiesis in Murine Rauscher Erythroleukemia (EMS-3) cells in microgravity.(STS-108/UF-1)

The EMS-3 cell line was derived originally from mice that were infected with the Rauscher virus – a murine virus that causes erythroleukemia. This cell line responds to the natural inducer of erythropoiesis (the formation of red blood cells), erythropoietin, and to other chemical inducers such as dimethyl sulfoxide (DMSO). The EMS-3 cells will be cultured on orbit and exposed to these inducers and the responsiveness of the cells to these inducers in microgravity will be compared to data from previous ground based Rotating Wall Vessel Bioreactor experiments. This research has a direct bearing on the future of long term human space flight as well as to ground based human disease. Data from these experiments will improve our knowledge of the effects of microgravity on the hematopoietic system and will suggest possible in flight countermeasures and treatments for ground based disease states.

O. Renal cell differentiation and hormone production in human renal cortical cells. (STS-108/UF-1)

Human renal cortical epithelial (HRCE) cells have flown in space shuttle missions STS-90, STS-106 and STS-105, and genomic and proteomic analyses were performed following return to Earth. As a consequence data was collected regarding the molecular expression of normal human kidney cells in microgravity and their potential in the production of renal hormones of biomedical significance. Continued studies in microgravity are expected to reveal additional information regarding the mechanisms involved in these responses. This experiment was aimed at examining the responses of normal human renal cells to a peptide sequence known to inhibit the vitamin D receptor under microgravity conditions, by evaluating cellular structure and assessing the synthesis of urokinase, vitamin D3, and other biomolecules. Long-term goals of this type of research include identification of genes that respond to microgravity, modeling of renal injury mechanisms, and production of kidney hormones of biopharmacological importance.

P. Evaluation of antibody production and proliferation by Human Lymphoid Tissue (HLT) cells in microgravity. STS-108/UF-1

The HLT cells were isolated from human tonsils derived from five donors for use during this experiment. Ground studies with human lymphoid tissues and cells in Rotating Wall Vessel (RWV) culture systems have demonstrated that some immune functions become impaired. Tonsil tissue blocks, or cells isolated from

tonsils, cultured in RWVs fail to respond to polyclonal activation or recall antigen challenge by increasing total or specific antibody production. However, if cells are challenged prior to culture in the RWVs, the responses will continue. We will examine both antibody production and cell proliferation of cells activated either during or before exposure to microgravity, to determine if the results observed in RWVs are in fact similar to those in true microgravity. We then hope to better understand how and why the cells are more or less affected by microgravity depending on their activation status.

Q. Tissue Response to Androgen Therapy and Microgravity (STS-107)
These studies involve the development of three-dimensional models of prostate carcinoma as a model for understanding the mechanisms of the disease. In microgravity a three-dimensional co-culture model was assembled comprised of bone stromal cells and human prostate carcinoma cells. The interaction of these hormonally-linked tissues provides the basis for understanding the mechanisms and progression of the disease. This was the first experiment to develop an in flight predictive model for androgen response in a microgravity environment.

V. Investigator Community

The Cellular Biotechnology investigator community extends throughout the USA and includes scientists with the NIH (a complete listing of investigator, projects, and publications is in the Appendix). The broad diversity of science supported by the Program and employing the bioreactor is illustrated in the expanse of the scientific publication venues. To date our scientists have published more than 300 papers and abstracts for publication and presentations since 1995. The publications describe ground-based and flight research findings with significance in 1) the engineering of cartilage and cardiac muscle, 2) tumor models that provide new strategies for drug development, 3) understanding the genetics of the cellular response to microgravity, 4) elucidating the pathology of infections such as HIV, lyme disease, protozoan infestation, and 5) propagation of tissues heretofore unavailable to the scientific community.

Included below is a list of the publication venues used by the Program investigators. Most of the research is published in discipline specific, non aerospace, peer reviewed journals. Some examples are: *Biomaterials, Anlytica Chimica Acta, Nature Medicine, Journal of Membrane Biology, FASEB (Federation of American Societies for Experimental Biology) Journal, Cancer Research, In Vitro Cellular & Developmental Biology – Animal, Journal of Immunology, Journal of Clinical Investigation, Pharmacological Research, Advances in Space Research, Applied Spectroscopy Journal, Gastroenterology, Immunopharmacology, International Reviews of Immunology, Journal of Immunotherapy, Oncogene, Sensors and Actuators B: Chemical, Sensors and Actuators A: Physical, Biotechnology Progress, Hepatology, Biotechnology Bioengineering, Cancer Metastasis Review, Cellular Transplantation, Cells and Materials., Endocrinology Proc., Immunology Newsletter, Journal of Biomolecular*

Structure and dynamics., Journal of Respiration, Cellular and Molecular Biology, Lung Cell. Mol. Physiol.Environ. Mol. Mutagenesis, Proceedings of the Indian .Academy of Science (Chem. Sci), Proceedings of the SPIE International Symposium on Biomedical Optics, Tissue Engineering, Transactions of the Orthopedic Research Society, Proceedings of the National Academy of Sciences(PNAS)

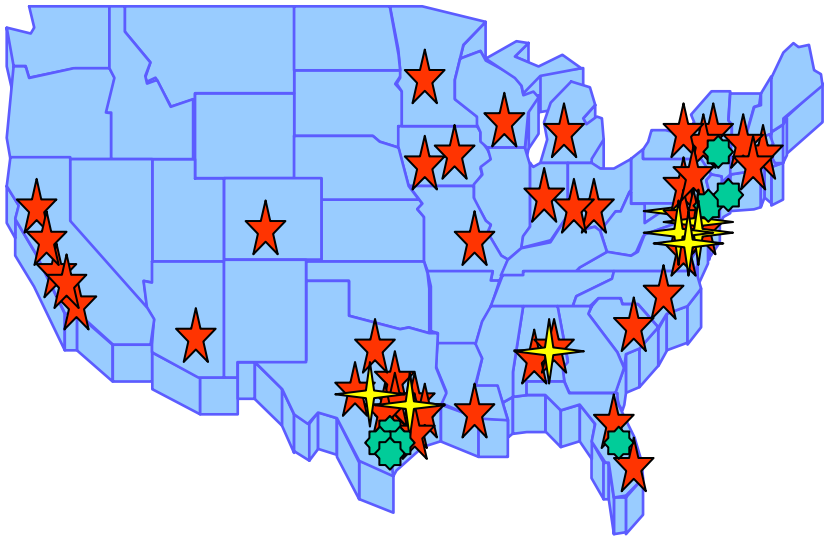
VI. Outreach

Science Community
Research Program Demographics

NRA Recipients

Government

Commercial



The Program is involved in extensive outreach activities in NASA, the science community, education, the government, and the community at large. The Biological Systems Office Outreach function is summarized below.

Science Outreach

Specific Science Customers
- Cell Science
- Tissue Engineering
- Applied Cell Biology
- Basic Cell Biology

Growing Science Community
- 55 currently funded extramural investigators
- More than 5,000 bioreactors in circulation

NASA Research Announcements
- 4 Biotechnology Cell Science Grant Opportunities

Research Grants
- NRAs - Microgravity, Life Sciences

NIH, TMC, NSBRI
In-house Field Center funding
National and International Meetings
ASCB, AACR, NanoSpace 2000, World Space Congress 2002,
COSPAR, IAA, World Biomaterials Congress
Research presentations/Invited Talks
ASGSB, Smart Systems 2000
AIAA, SIVB, NCI/NASA
Dedicated Symposia/Conference Co-chairs/Panel Members
ASCB, SIVB
STAIF, 1st International Symposium on Microgravity Research and
Applications in Physical Sciences
Peer Reviewed Publications
Investigators Working Group Meeting
Annual review of NRA grant recipients' research
Historical Data:
1994 - Investigator group of 14 scientists attend
1998 - Investigator group exceeds 75 scientists
1999 - Over 100 attendees, 26 presentations, 3 exhibitors
2000 - 106 attendees, 34 presentations, 3 commercial exhibitors
2001 – 187 attendees, 63 presentations, 8 exhibits
2002 - 161 attendees, 61 presentations, 6 exhibits in Palo Alto, CA
2003- 166 attendees, 64 presentations, 6 exhibits (Estimated)

Academic Outreach

University faculty appointments

University of Texas Health Science Center, University of Texas Medical Branch and Rice University - Pellis
University of Houston - Anderson
Tulane University – Goodwin
University of Texas Health Science Center, University of Texas Medical Branch - Dr. Diane Byerly
University of Texas Health Science Center, University of Texas Medical Branch - Dr. Marguerite Sognier

Courses taught

Space Physiology - Biotechnology (UTMB-Galveston and UTHSC-Houston) - Pellis
Cancer Immunology and Biology - Pellis
Organic Chemistry - Anderson
Space Physiology- Goodwin

Textbook contributions

Cancer Cell Biology and Immunology in 3 surgery textbooks - Pellis
Basic and Applied Space Cell Biology (in preparation) - Pellis and Jessup

Future development

Coursework at Texas A&M @ Galveston

Research with the new Center for Microencapsulation and Drug Delivery at Texas A&M (TAMU)

Program Degree Accomplishments

PhD. Aerospace Engineering Sciences - Byerly
PhD. Physiology and Bioengineering Sciences, to be completed Dec. 2002 - Goodwin
PhD. coursework @ UTMB - Lundquist

Guest Researchers

Visiting Scientists - Pellis, Gonda, Goodwin
USRA - Morrison, Gonda, Goodwin, Byerly
NASA Faculty Fellowship Program- Byerly

Graduate Students/ Summer Students Mentorship

Immunology - Pellis
In Vitro Bone Model - Gonda
Cell Science – Gonda
Skeletal Muscle- Byerly (T. Fowler)
Cardiac Muscle- Byerly (S. Jones)

University Research Collaborations

Microencapsulation flight experiments – TAMU Center for Space Power

Microencapsulation animal testing – TAMU School of Veterinery Medicine

Bioreactor – stem cell culture systems for vaccine production - UTMBG

Industry Outreach

Synthecon, Inc.
NASA-designed bioreactors commercially available
Celdyne, Inc.
Hydrodynamic Focusing Bioreactors commercially available
Viragen, Inc.
Using bioreactors for enhanced production of high value biomolecules
Tanox, Inc.
Use of the Bioproduct Recovery System for monoclonal antibodies
Stratagene
Collaboration for development of 3-D transgenic reporter models
Sulzer
Development of 3-D bone models
Fisk Ventures - Stelsys
* In Vitro cell models
* New drug development
* Drug testing
* Liver Assist Device

Wyeth-Lederle
Pediatric vaccine development

Community Outreach

NASA's Public Affairs Office
Houston Livestock Show and Rodeo
JSC's *Benefits of Space* Trailer Exhibit
Technology Showcases & Panels
National Conventions
American Association of Retired Persons, American Public Health Association, Media Forum on Aging Research, Mexican American Engineers & Scientists 2001

Media
Radio interviews
Discovery Channel television interview
Presentations to elementary and secondary schools
Invited talks
Volunteer - Engineering Week
High school science fair judges
Presentations to community organizations
Greater Houston Partnership, Rotary, business groups and political groups

VI. Technology Transfer

Patents: Bioreactor /Cell Science
Twenty patents issued (19 licensed)
Five applications pending
Microencapsulation - Three patents issued (1 licensed)
-Three patents pending
Cancer Cell Testing - One patent issued (1999)
- Two disclosures submitted

2000 Disclosures:
Bioreactor /Cell Science
Cytokine & Interferon - (MSC-23276-1)
Microencapsulation
Microcapsule Flow Sensor (MSC-23277-1)

Patent Licenses: Synthecon - STLV, HARVs
VivoRx - Bioreactor use for growing pancreatic cells for encapsulation and transplantation
Celdyne - Hydrodynamic Focusing Bioreactor
Fisk Ventures - Bioreactor designs (4)
(Stelsys Inc) - Fields of Use: Liver Assist Device
Liver cells and products
Renal cells & products
Drug testing & toxicity on cells

Space Act Agreements:

- Juvenile Diabetes Foundation
- Viragen - Interferon production
- Fisk Ventures - bioreactor & cell applications includes re-imburseable flight experiments
- Wyeth-Lederle Drug Study - Procure, expand, maintain and cryopreserve lung mesenchymal cells to study the efficacy of candidate drugs in collaboration with Wyeth-Lederle pharmaceutical company.

VII. The Future

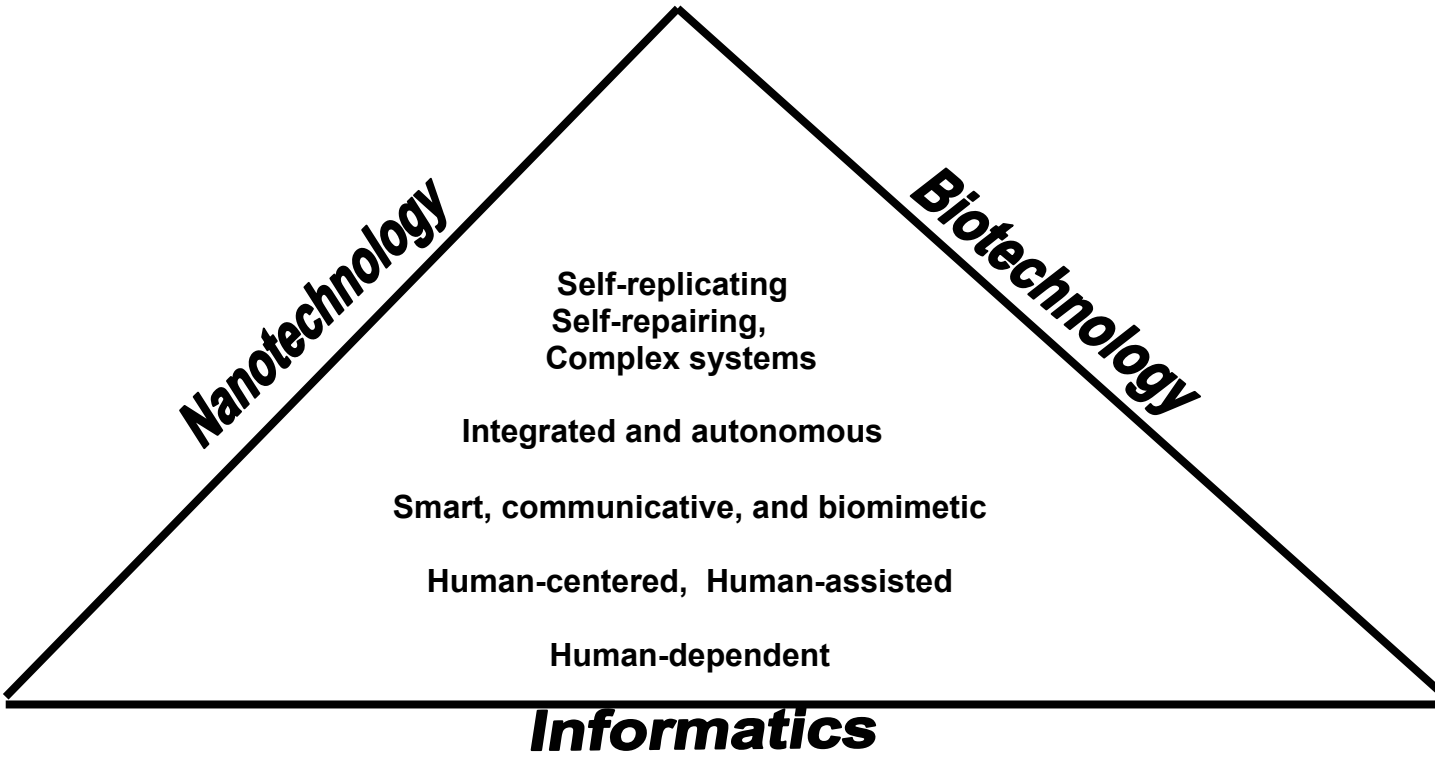
Biologically Inspired Technology Research (BITR)

- Micro and Nanosphere Technology
- Enhanced Photodynamic Therapy (PDT) for treating cancer
- Neovascularization and tissue growth in orthopedic implants
- Microencapsulated drugs - extend shelf-life -> long duration missions
  - Alternative drug delivery for crewmembers
- Quantitative applications in petrochemical industry

Nanotechnology

- Integrated with living systems
- Targeted gene expression
- Lab on a chip - ground applications and flight experiments
- Biologically based sensors
- Physiologically balanced cell culture systems
- Organoid engineering

The next generation of technologies will draw from evolving knowledge in nanotechnologies, biotechnology, and informatics.



APPENDICES

Appendix 1 Contractor Contributions to the Program

Wyle Life Sciences

The mission of the Biotechnology Program is to use microgravity as a tool to overcome gravity-based limitations in biotechnology processes for cell biology and tissue engineering, in order to advance our understanding of basic cellular processes as they relate to the assembly and propagation of tissues that may form models of human disease and provide tissues for replacement therapy. The activities of this program are driven by the requirements set forth by the user community of academic, commercial, and governmental scientific investigators. These requirements are dynamic and follow the state-of-the-art experiment strategies that use microgravity and NASA technology to provide unique cell culture environments.

The scientific investigators' requirements dictate the design and development of bioreactors and supporting instrumentation necessary for continuing a robust ground-based research program, in addition to flight instrumentation and experimental procedures. Design and development of a dedicated facility on the International Space Station (ISS) is dictated by the nature of the flight experiments and the flight instrumentation. It is anticipated that the development of experiment-specific instrumentation and the ISS facility will provide an envelope of resources that accommodate a wide community of biotechnological experiments.

The following describes the activities performed within the Biotechnology Program, for which the contractor, Wyle Laboratories has overall responsibility. This work is performed so that all ground-based and flight hardware manifested by NASA, and the associated data analyses and compilations, are successfully accomplished. These activities will lead to the establishment of a broad-application biotechnology facility on ISS.

- Design, develop, fabricate, and test hardware for a facility aboard ISS to accommodate a broad range of biotechnology experiments in cell culture, tissue engineering, and protein crystal growth.

- Design, develop, fabricate, and test bioreactor systems to sustain growth of high-fidelity, three-dimensional tissues in ground-based and space flight environments, including all life support systems necessary to support cell metabolism and growth while minimizing crew time and expendables.

- Integrate flight experiments, perform all certifications, and formulate documentation for Shuttle, Mir, and ISS.

- Perform fluid dynamic analysis of rotating and reciprocating flow systems to provide infusion, perfusion, and uniform composition of nutrient media in bioreactors for unit and microgravity operation.

- Design, develop, implement and test real-time process control algorithms to maintain steady-state conditions in bioreactors.

- Design, develop, implement and test chemical, physical or biological sensors for process control in bioreactors.

- Develop, fabricate, manifest, and integrate hardware for space flight on Space Shuttle, Mir and ISS.

- Modify hardware and experiment conditions in order to successfully run NRA/NIH-sponsored proposed experiments in ground-based and flight bioreactors.

- Culture tissues in bioreactors to test models for cell differentiation, cancer growth and metastasis, locomotion of immune cells, and HIV pathogenesis in support of NRA/NIH-sponsored proposed experiments.

- Analyze cultured tissues using contemporary scientific technologies and assays.

- Transition research from the scientific community to flight experiments.

- Provide project and contract management to meet the goals of the Biotechnology Program

Universities Space Research Association

Dr. Marguerite Sognier- Skeletal and cardiac tissue equivalent muscle models, microwave irradiation effects, stem cell isolation and differentiation into three-dimensional models

Dr Alamelu Sundaresan –

Primary areas of research:

- Lymphocyte functions in Microgravity
- Ground Culture Analogs using both Human and Mouse Systems.

Other research areas:

- Ontogeny and Embryogenesis of the Fish R.marmoratus in Microgravity
- Nutritional Immunomodulation in Microgravity
- Tumor Models in Microgravity
- Virulence of M.tuberculosis in Microgravity
- Differential Gene Expression in Microgravity.

Futron Corporation

Biological Systems Office website development

Principal Investigators & Projects

Investigator	Institution	Project Title
1989		
Brown, R Malcolm.	University of Texas	Biosynthesis of Cellulose under Microgravity Conditions
1991		
Jessup, J Milburn, M.D.	New England Deaconess Hospital	Three-Dimensional Modeling of Human Colon Tissue
1992		
Becker, Jeanne L., Ph.D.	University of South Florida	Evaluation of Ovarian Tumor Cell Growth and Gene Expression
Hartzell, Charles, R., Ph.D.	Alfred I. duPont Institute	Excitable Cells and Growth Factors under Microgravity Conditions
Ingram, Marylou.	Huntington Medical Research Institutes	Sensitized Lymphocytes for Tumor Therapy Grown in Microgravity
Lelkes, Peter I., Ph.D.	University of Wisconsin, Milwaukee	Neuro-endocrine Organoid Assembly in Vitro
Palsson, Bernhard, O.	University of California, San Diego	Shear Sensitivities of Human Bone Marrow Cultures
Saltzman, W. Mark, Ph.D.	Cornell University	Enhancement of Cell Function in Culture by Controlled Aggregation
1993		
Jessup, J Milburn, M.D.	New England Deaconess Hospital	Three-Dimensional Tissue Interactions in Colorectal Cancer Metastasis
Scharp, David W.	Washington University School of Medicine	Culture of Porcine Islet Tissue: Evaluation of Microgravity Conditions(THIS GRANT WAS TERMINATED AT THE REQUEST OF THE PI.)
1994		
Freed, Lisa E., M.D., Ph.D.	Massachusetts Institute of Technology	Microgravity Studies of Cell-Polymer Cartilage Implants
O'Connor, Kim C., Ph.D.	Tulane University	Insect-Cell Cultivation in the NASA High Aspect Rotating-Wall Vessel
1995		
Ayyaswamy, Portonovo S., Ph.D.	University of Pennsylvania	The Use of Bioactive Glass Particles as Microcarriers in Microgravity Environment
Bhatnagar, Rajendra S., Ph.D.	University of California, San Francisco	Expansion and Differentiation of Cells in Three-Dimensional Matrices Mimicking Physiological Environments
Chung, Leland W., Ph.D.	University of Virginia	Microgravity Simulated Prostate Cell Culture
Cote, Gerard L., Ph.D.	Texas A&M University	Noninvasive Near-Infrared Sensor for Continual Cell Glucose Measurement
Dimitrijevich, S. Dan, Ph.D.	Univ. of N. Texas Health Science Ctr, Fort Worth	The Effect of Microgravity on the Human Skin Equivalent
Dirksen, Ellen R., Ph.D.	University of California, Los Angeles	Use of Microgravity-Based Bioreactors to Study Intercellular Communication in Airway Cells
Durzan, Don J.	University of California, Davis	Microgravity Thresholds for Anti-Cancer Drug Production on Conifer Cells
Frangos, John A., Ph.D.	University of California, San Diego	Role of Fluid Shear on 3-D Bone Tissue Culture

Freed, Lisa E., M.D., Ph.D.	Massachusetts Institute of Technology	Microgravity Tissue Engineering
Goodwin, Thomas J., M.A	NASA - Johnson Space Center	Lymphocyte Invasion Into Tumor Models Emulated Under Microgravity Conditions In Vitro
Hammond, Timothy G., Ph.D.	Tulane University Medical Center	Differentiation of Cultured Normal Human Renal Epithelial Cells in Microgravity
Heath, Carole A., Ph.D.	Iowa State University	Determining the Conditions Necessary for the Development of Functional Replacement Cartilage Using a Microgravity Reactor
Helmstetter, Charles E.	Florida Institute of Technology	Baby Machine Analysis of Cellular Gravity Sensitivity
Hughes, John H., Ph.D.	Ohio State University	The Effects of Microgravity on Viral Replication
Jessup, J Milburn, M.D.	Univ. of Texas Health Science Center-San Antonio	Growth, Metabolism, and Differentiation of MIP-101 Carcinoma Cells
Johnson, Philip C., M.D.	Johnson University of Texas Medical School	Use of Rotating Wall Vessel (RWV) to Facilitate Culture of Norwalk Virus - Johnson
Kraus, William E., M.D.	Duke University Medical Center	Regulation of Skeletal Muscle Development and Differentiation In Vitro by Mechanical and Chemical Factors
Lelkes, Peter I., Ph.D.	University of Wisconsin Medical Center	Avian Blood Formation in Space
Levine, Elliot M., Ph.D.	The Wistar Institute	Multidisciplinary Studies of Cells, Tissues, and Mammalian Development in Simulated Microgravity
Martin, Andreas, M.D.	Mount Sinai Medical Center	Thyroid Follicle Formation in Microgravity: Three-Dimensional Organoid Construction in a Low-Shear Environment
Murhammer, David W., Ph.D.	University of Iowa	Continuous, Noninvasive Monitoring of Rotating Wall Vessels and Application to the Study of Prostate Cancer
O'Connor, Kim C., Ph.D.	Tulane University	Insect-Cell Cultivation in Simulated Microgravity
Oefinger, Paul E.	University of Texas Medical School	Use of Rotating Wall Vessel (RWV) to Facilitate Culture of Norwalk Virus
Pellis, Neal R., Ph.D.	NASA - Johnson Space Center	Microgravity and Immunosuppression: A Ground-Based Model in the Slow Turning Lateral Vessel Bioreactor
Quesenberry, Peter J., M.D.	University of Massachusetts Medical Center	Stem Cell Expansion in Rotating Bioreactors
Stewart, F. Marc, M.D.	University of Massachusetts Medical Center	Influence of Microgravity Conditions on Gene Transfer Into Expanded Populations of Human Hematopoietic Stem Cells
Towe, Bruce C., Ph.D.	Arizona State University	Development of Microflow Biochemical Sensors for Space Biotechnology
1996		
Gonda, Steve R., Ph.D.	NASA - Johnson Space Center	Space Bioreactor Bioproduct Recovery System
Pellis, Neal R., Ph.D.	NASA - Johnson Space Center	Microgravity Induced Changes in Lymphocyte Movement Through Interstitium
Sytkowski, Arthur J., M.D.	Beth Israel Deaconess Medical Center	Gravitational Effects on Signal Transduction
1997		
Cameron, Donald F., Ph.D.	University of South Florida	Development of an Insulin Secreting, Immunoprivileged Cell-Cell Aggregate Utilizing the NASA Rotating Wall Vessel
Chittur, Krishnan K.	University of Alabama, Huntsville	Infrared Signatures for Mammalian Cells in Culture
Frangos, John A., Ph.D.	University of California, San Diego	Microgravity In Vitro Model of Bone: Flow Effects
Gonda, Steve R., Ph.D.	NASA - Johnson Space Center	Space Bioreactor Media Reclamation System
Gonda, Steve R., Ph.D.	NASA - Johnson Space Center	Space Bioreactor Media Reclamation System and Bioproduct Recovery System

Gonda, Steve R., Ph.D.	NASA - Johnson Space Center	Hydrodynamic Focusing Bioreactor
Grimm, Elizabeth A., Ph.D.	University of Texas M.D. Anderson Cancer Center	Application of Bioreactor Technology for Analysis and Counter Measure Development of Microgravity Induced Suppression of Innate Immunity
Hammond, Timothy G., Ph.D.	Tulane University Medical Center	Production of 1-25-diOH D3 by Renal Epithelial Cells in Simulated Microgravity Culture
Hu, Wei-Shou	University of Minnesota	Self-Assembly of Hepatocyte Spheroids in Microgravity
Jessup, J Milburn, M.D.	University of Pittsburgh Medical Center	Use of NASA Bioreactor to Study Cell Cycle Regulation
Richmond, Robert C.	NASA - Marshall Space Flight Center	Heterozygous Ataxia-Telangiectasia Human Mammary Cells as a Microgravity- Based Model of Differentiation and Cancer Susceptibility
Saltzman, W. Mark, Ph.D.	Cornell University	Enhancement of Cell Function in Culture by Controlled Aggregation Under Microgravity
Savary, Cherylyn A., Ph.D.	University of Texas M.D. Anderson Cancer Center	Use of NASA Bioreactors in a Novel Scheme for Immunization Against Cancer
Schwartz, William J.	University of Massachusetts Medical School	Microgravity and the Biology of Neural Stem Cells
Smolka, Adam J., Ph.D.	Medical University of South Carolina	Gastric Mucosal Cell Culture in Simulated Microgravity
Sytkowski, Arthur J., M.D.	Beth Israel Deaconess Medical Center	Production of Recombinant Human Erythropoietin by Mammalian Cells Cultured in Simulated Microgravity
Wood, H. Alan	Cornell University	The Effects of Microgravity/Low Shear on Glycosylation and Eukaryotic DNA Virus Replication
Wu, J. H. David.	University of Rochester	Ex Vivo Hemopoieses in a Three-Dimensional Human Bone Marrow Culture under Simulated Microgravity
Yoffe, Boris, Ph.D.	Baylor College of Medicine	Liver Tissue Engineering in Microgravity Environment
1998		
Lelkes, Peter I., Ph.D.	Drexel University	Effect of Spaceflight on Adrenal Medullary Function
1999		
Belovich, Joanne M.	Cleveland State University	An Accoustically Assisted Bioreactor for Terrestrial and Microgravity Applications
Chopra, Vimlarani, Ph.D.	University of Texas Medical Branch, Galveston	Differentiation of 3-Dimensional Co-cultures of Myofibroblasts, Preneoplastic Epithelial and Mononuclear Cells
Chung, Leland W., Ph.D.	University of Virginia	Modeling Prostate Cancer Skeletal Metastasis and Gene Therapy
Cote, Gerard L., Ph.D.	Texas A&M	Investigation of Neuronal Physiology in Simulated Microgravity using Smart Fluorescent Microcarriers and Bulk Near Infrared Sensors
DiRuggiero, Jocelyne, Ph.D.	University of Maryland	Microbial Resistance to Solar Radiation: DNA Damage and Application of Repair Enzymes in Biotechnology
Frangos, John A., Ph.D.	University of California, San Diego	Novel Strategy for Tridimensional In Vitro Bone Induction
Freed, Lisa E., M.D., Ph.D.	Massachusetts Institute of Technology	Microgravity Tissue Engineering
Gonda, Steve R., Ph.D.	NASA - Johnson Space Center	A Microgravity-based, Three-dimensional Transgenic Cell Model to Quantify Genotoxic Effects in Space
Grimm, Elizabeth A., Ph.D.	University of Texas MD Anderson Cancer Center	Application of Bioreactor Technology for a Preclinical Human Model of Melanoma
Helmstetter, Charles E.	Florida Institute of Technology	New Cell Culture Technology
Kraus, William E., M.D.	Duke University Medical Center	Differentiation and Maintenace of Skeletal and Cardiac Muscle in Simulated Microgravity
Kulkarni, Anil D.	University of Texas Health Science Center -Houston	Nutritional Immunomodulation in Microgravity: Application of Ground-Based In Vivo and In Vitro Bioreactor Models to Study Role and Mechanisms of Supplemental Nucleotides

Lelkes, Peter I., Ph.D.	Drexel University	PC12 Pheochromocytoma Cells: A Proven Model System for Optimizing 3-D Cell Culture Biotechnology in Space
Malak, Henryk.	Microcosm, Inc.	Cellular Oxygen and Nutrient Sensing in Microgravity using Time-resolved Fluorescence Microscopy
McCabe, Laura R.	Michigan State University	Microgravity Regulation of Oncogene Expression and Osteoblast Differentiation
Murhammer, David W., Ph.D.	University of Iowa	Monitoring and Control of Rotating Wall Vessels and Application to the Study of Prostate Cancer
Nickerson, Cheryl A., Ph.D.	Tulane University	Effect of Simulated Microgravity on Gene Expression in the Enteric Pathogen Salmonella Typhimurium
Rajan, Arun S., M.D.	Baylor College of Medicine	Islet Cell Assembly and Function in a NASA Microgravity Bioreactor
Rodgers, Victor G.	University of Iowa	Evaluating Oxidative Stress in Virally-infected Cells in Simulated Microgravity
Rutzky, Lynne P.	University of Texas Health Science Center	Impact of Microgravity on Immunogenicity Associated with Biostructural Changes in Pancreatic Islets
Sah, Robert L.	University of California, San Diego	Cartilage Tissue Engineering: Circumferential Seeding of Chondrocytes Using Rotating Reactors
Spaulding, Glenn F., M.D.	Clear Lake Medical Foundation, Inc.	Application of pH, Glucose, and Oxygen Biosensors to NASA Rotating Culture Vessels
Traycoff, Christie M., Ph.D.	Indiana Cancer Research Institute	Self Renewal Replication of Hematopoietic Stem Cells in Microgravity
2000		
Hammond, Timothy G., Ph.D.	Tulane University Medical Center	Neurolab Reflight
Lelkes, Peter I., Ph.D.	Drexel University	Altered Signal Transduction and Differential Gene Expression in PC12 Phochromocytoma Cells Cultured in "Simulated Microgravity"
Sah, Robert L.	University of California, San Diego	Fabrication and Growth of Engineered Tissues: Articular Cartilage with Biological and Functional Stratification
2001		
Akins, Robert E., Ph.D.	Alfred I. duPont Hospital for Children	Cell: Cell Mediated Assembly of Cardiac Tissue in Microgravity environments
Almeida-Porada, Graca, M.D., Ph.D.	University of Nevada	Stem Cell Plasticity Under Simulated Microgravity
Becker, Jeanne L., Ph.D.	University of South Florida	3-D Growth Effects on Drug Resistance in Human Ovarian Tumor Cells
Fertala, Andrzej, Ph.D.	Thomas Jefferson University	Genetically Engineered Collagen II for Smart Biomaterials
Folch, Albert, Ph.D.	University of Washington	Microarrays of Cellular Membrane Patches for In-Flight Studies of ion Channel Function
Hammond, Timothy G., Ph.D.	Tulane University Medical Center	Transcription Factors Mediating Gene Expression Changes During Renal Cell Rotating Wall Vessel Culture
Harden, James L., Ph.D.	John Hopkins University	A Modular Library of Self-Assembling Artificial Proteins for Three-Dimensional Tissue Culture
Inverardi, Luca, M.D.	University of Miami School of Medicine	Cell Transplantation Therapy for Diabetes Utilizing Immunoprivileged Sertoli-Islet Cell Aggregates (SICA)
Jessup, J Milburn, M.D.	Georgetown University Medical Center	Gene Expression of Human Colorectal Carcinoma in Microgravity
Ma, Wu, Ph.D.	Naval Research Laboratory	Neurogenesis in a Cell-Hydrogel-Bioreactor System: Forming Neuronal Networks in Microgravity
Marr, W.M. David	Colorado School of Mines	A Novel Colloidal Microfluidics Platform for Spaceborne Micro Total Analysis Systems
O'Connor, Kim C., Ph.D.	Tulane University	Spatial Organization Within Prostate Cancer Spheroids

Ramsey, John M, Ph.D.	Oak Ridge National Laboratories	Automated Microfluidic Devices for Monitoring Biological Systems in Space
Rutzky, Lynne P.	University of Texas Health Science Center	Effects of Microgravity on Pancreatic Islet Xenotransplantation, Vascularization and Stem Cell Growth
Saporta, Samuel, Ph.D.	University of South Florida	Creation and Transplantation of Immunoprivileged Sertoli- Neuron-Aggregated-Cells (SNACs) for the Treatment of Parkinson's Disease
Sytkowski, Arthur J., M.D.	Beth Israel Deaconess Medical Center	Growth Factor Receptor Function and Cell Differentiation in a Low-Shear Environment
Towe, Bruce C., Ph.D.	Arizona State University	A Microfluidic Bioreporter for Explanatory Probes
Wu, J. H. David.	University of Rochester	Circadian Rhythm and Control of Hematopoiesis
Yoffe, Boris, Ph.D.	Baylor College of Medicine	Liver Tissue Engineering in Microgravity Environment

Flight Experiments

Becker, Jeanne L, Ph.D.	STS-105/7A.1	Evaluation of Ovarian Tumor Cells Growth and Gene Expression
Chung, Leland W, Ph.D.	STS-107	Tissue Response to Androgen Therapy and Microgravity
Freed, Lisa E, Ph.D.	STS-79/Mir-3	Cartilage Development in the Bioreactor
Gonda, Steve R, Ph.D.	STS-89/Mir-7	Biotechnology System Data Acquisition and Control System (DACS)
Gonda, Steve R, Ph.D.	STS-84/Mir-5	Biotechnology System Data Acquisition & Control System (DACS)
Goodwin, Thomas J	STS-62	Growth of Mammalian Cells in Unfacilitated Mass Transfer
Hammond, Timothy G, Ph.D.	STS-108/UF-1	Renal Biopharmacological and Genetic Expression Model in Microgravity
Hammond, Timothy G, Ph.D.	STS-105/7A.1	Renal Cell Differentiation and Hormone Production from Human renal cortical cells
Hammond, Timothy G, Ph.D.	STS-90	Human Renal Tubular Cells
Hammond, Timothy G, Ph.D.	STS-86/Mir-6	Rat Renal Tubular Cells
Jessup, J. Milburn, M.D.	STS-105/7A.1	Use of NASA Bioreactor to Study Cell Cycle Regulation Mechanisms of Colon Carcinoma Metastasis in Microgravity
Jessup, J. Milburn, M.D.	STS-70	Growth, Metabolism, and Differentiation of MIP-101 Carcinoma Cells
Jessup, Milburn, M.D.	STS-85	Growth, Metabolism, and Differentiation of MIP-101 Carcinoma Cells (Reflight of STS-70)
Lelkes, Peter I, Ph.D.	STS-86/Mir-6	Neuroendocrine Development in Microgravity (PC-12)
Lelkes, Peter I, Ph.D.	STS-105/7A.1	PC12, Pheochromocytoma Cells: A Proven Model System for Optimizing 3-D Cell Culture Biotechnology in Space
Levine, Elliot M, Ph.D.	STS-89/Mir-7	Biotechnology System Coculture of Endothelial Cells and Human Breast Carcinoma
Morrison, Dennis	STS-108/UF-1	Microencapsulation Electrostatic Processing System
Morrison, Dennis	STS-105/7A.1	Microencapsulation Electrostatic Processing System
Morrison, Dennis	STS-67	Microencapsulation
Morrison, Dennis	STS-95	Microencapsulation Electrostatic Processing System

Appendix 3
Cellular Biotechnology Program – Journals and Abstracts

1992

Brown RM, Kudlicka K, Cousins SK, Nagy R.
Gravity effects on cellulose assembly.
Am J Bot. 1992 Nov; 79(11):1247-58.

Goodwin TJ, Jessup JM, Wolf DA.
Morphologic differentiation of colon carcinoma cell lines HT-29 and HT-29KM in rotating-wall vessels.
In Vitro Cell Dev Biol. 1992 Jan; 28A(1):47-60.

Lelkes PI, Unsworth BR.
Heterotypic co-cultures of rat adrenal medullary parenchymal and endothelial cells from organoids in vitro.
The American Society for Cell Biology 32nd annual meeting.
Denver, CO, USA.Nov 15-19 1992.
Mol Biol Cell. 1992 Sep;3 Suppl:290a.

1993

Becker JL, Prewett TL, Spaulding GF, Goodwin TJ.
Three-dimensional growth and differentiation of ovarian tumor cell line in high aspect rotating-wall vessel: morphologic and embryologic considerations.
J Cell Biochem. 1993 Mar; 51(3):283-9.

Freed LE, Vunjak-Novakovic G, Langer R.
Cultivation of cell-polymer cartilage implants in bioreactors.
J Cell Biochem. 1993 Mar; 51(3):257-64.

Freed LE, Marquis JC, Nohria A, Emmanual J, Mikos AG, Langer R.
Neocartilage formation in vitro and in vivo using cells cultured on synthetic biodegradable polymers.
J Biomed Mater Res. 1993 Jan; 27(1):11-23.

Jessup JM, Kim JC, Thomas P, Ishii S, Ford R, Shively JE, Durbin H, Stanners CP, Fuks A, Zhou H.
Adhesion to carcinoembryonic antigen by human colorectal carcinoma cells involves at least two epitopes.
Int J Cancer. 1993 Sep 9; 55(2):262-8.

Jessup JM, Petrick AT, Toth CA, Ford R, Meterissian S, O'Hara CJ, Steele G, Thomas P.
Carcinoembryonic antigen: enhancement of liver colonisation through retention of human colorectal carcinoma cells.
Br J Cancer. 1993 Mar; 67(3):464-70.

Jessup JM, Goodwin TJ, Spaulding GF.
Prospects for use of microgravity-based bioreactors to study three-dimensional host-tumor interactions in human neoplasia.
J Cell Biochem. 1993 Mar; 51(3):290-300.

Spaulding GF, Jessup JM, Goodwin TJ.
Advances in cellular construction.
J Cell Biochem. 1993 Mar; 51(3):249-51.

Lelkes PI, Ramos EM, Chick DM, Liu J, Unsworth BR.
Space flight alters catecholmine synthesizing enzyme expression and activity in the rat adrenal medulla.
The American Society for Cell Biology 33rd annual meeting.
New Orleans, LA, USA.Dec 11-15 1993.
Mol Biol Cell. 1993 Oct;4 Suppl:109a.

1994

Becker JL.
Womens health issues and space-based medical technologies.
Earth Space Rev. 1994 Apr-Jun; 3(2):15-9.

Berthiaume F, Frangos JA.
Fluid flow increases membrane permeability to merocyanine 540 in human endothelial cells.
Biochim Biophys Acta. 1994 Apr 20; 1191(1):209-18.

Freed LE, Vunjak-Novakovic G, Biron R, Eagles DB, Lesnoy DC, Barlow SK, Langer R.
Biodegradable polymer scaffolds for tissue engineering.
Biotechnology (N Y). 1994 Jul; 12(7):689-93.

Freed LE, Grande DA, Lingbin Z, Emmanual J, Marquis JC, Langer R.
Joint resurfacing using allograft chondrocytes and synthetic biodegradable polymer scaffolds.
J Biomed Mater Res. 1994 Aug; 28(8):891-9.

Freed LE, Vunjak-Novakovic G, Marquis JC, Langer R.
Kinetics of chondrocyte growth in cell-polymer implants.
Biotechnol Bioeng. 1994 Mar 25; 43(7):597-604.

Garrison LA, Frangos JA, Geselowitz DB, Lamson TC, Tarbell JM.
A new mock circulatory loop and its application to the study of chemical additive and aortic pressure effects on hemolysis in the Penn State electric ventricular assist device.
Artif Organs. 1994 May; 18(5):397-407.

Hillsley MV, Frangos JA.
Bone tissue engineering: the role of interstitial fluid flow.
Biotechnol Bioeng. 1994 Mar 25; 43(7):573-81.

Ishii S, Steele G, Ford R, Paliotti G, Thomas P, Andrews C, Hansen HJ, Goldenberg DM, Jessup JM.
Normal colonic epithelium adheres to carcinoembryonic antigen and type IV collagen.
Gastroenterology. 1994 May; 106(5):1242-50.

Jessup JM, Brown K, Ishii S, Ford R, Goodwin TJ, Spaulding GF.
Simulated microgravity does not alter epithelial cell adhesion to matrix and other molecules.
Adv Space Res. 1994 ; 14(8):71-6.

Kuchan MJ, Frangos JA.
Role of calcium and calmodulin in flow-induced nitric oxide production in endothelial cells.
Am J Physiol. 1994 Mar; 266(3 Pt 1):C628-36.

Kuchan MJ, Jo H, Frangos JA.
Role of G proteins in shear stress-mediated nitric oxide production by endothelial cells.
Am J Physiol. 1994 Sep; 267(3 Pt 1):C753-8.

Lelkes PI, Ramos EM, Chick DM, Liu J, Unsworth BR.
Microgravity decreases tyrosine hydroxylase expression in rat adrenals.
FASEB J. 1994 Nov; 8(14):1177-82.

Tsao YM, Boyd E, Wolf DA, Spaulding GF.
Fluid dynamics within a rotating bioreactor in space and earth environments.
J Spacecr Rockets. 1994 ; 1994 Nov-Dec; 31(6):939-43.

Fitzgerald WS, Craig JN, Spaulding GF, Jessup JM, Goodwin TJ.
Expression of carcinoembryogenic antigen in MIP-101 colon carcinoma cells in rotating-wall vessel culture.
The American Society for Cell Biology 34th annual meeting.
San Francisco, CA, USA.Dec 10-141994.
Mol Biol Cell. 1994 Oct;5 Suppl:483a.

Francis KM, O'Connor KC, Blake D, Caldwell DR, Spaulding GF.
Growth and structure of corneal tissue in simulated microgravity.
ESACT/JAACT Meeting 1994.
Veldhoven, The Netherlands.Sep 12-161994.
Cytotechnology. 1994;14 Suppl 1:7.16.

Galvan DL, Wankowski DM, Bacciao R, Dillinger A, Karmiol S, Hammond TG, Lelkes PI.
Human renal epithelial cells in culture differentiate under simulated microgravity.
The American Society for Cell Biology 34th annual meeting.
San Francisco, CA, USA.Dec 10-141994.
Mol Biol Cell. 1994 Oct;5 Suppl:120a.

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Botella JR, Arteca RN, Frangos JA.
A mechanical strain-induced 1-aminocyclopropane-1-carboxylic acid synthase gene.
Proc Natl Acad Sci U S A. 1995 Feb 28; 92(5):1595-8.

Chung H, Arnold MA, Rhiel M, Murhammer DW.
Simultaneous measurement of glucose and glutamine in aqueous solutions by near infrared spectroscopy.
Appl Biochem Biotechnol. 1995 Feb; 50(2):109-25.

Freed LE, Vunjak-Novakovic G.
Cultivation of cell-polymer tissue constructs in simulated microgravity.
Biotechnol Bioeng. 1995 May 20; 46(4):306-13.

Hung R.J., Tsao Y.D., Gonda S.R.
Time Sequence Evolution of Human Cell Deformation in Micro- and Hypergravity.
Microgravity Quarterly 5: 91-99 (1995).

Klein-Nulend J, Van DE, Plas A, Semeins CM, Ajubi NE, Frangos JA, Nijweide PJ, Burger EH.
Sensitivity of osteocytes to biomechanical stress in vitro.
FASEB J. 1995 Mar; 9(5):441-5.

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Tissue engineering: Biomedical application.
Tissue Eng. 1995 ; 1(2):151-61.

Manolopoulos VG, Samet MM, Lelkes PI.
Regulation of the adenylyl cyclase signaling system in various types of cultured endothelial cells.
J Cell Biochem. 1995 Apr; 57(4):590-8.

Martin A, Matsuoka N, Concepcion ES, Davies TF.
Endogenous antigen presentation by autoantigen-transfected Epstein-Barr virus-lymphoblastoid cells: T cell receptor N-region hydrophobicity relates to thyroid antigen recognition.
Autoimmunity. 1995 ; 21(4):223-30.

Okhuysen PC, Jiang X, Ye L, Johnson PC, Estes MK.
Viral shedding and fecal IgA response after Norwalk virus infection.
J Infect Dis. 1995 Mar; 171(3):566-9.

Risin D, Kleinerman ES, Umezu Y, Pizzini RP, Balch CM, Pellis NR.
Impairment of lymphocyte locomotion in the tumor microenvironment and the effect of systemic immunotherapy with liposome-encapsulated muramyl-tripeptide-phosphatidylethanolamine.
Cancer Immunol Immunother. 1995 Jan; 40(1):57-64.

Rossitti S, Frangos JA, Girard PR, Bevan J.
Regulation of vascular tone.
Can J Physiol Pharmacol. 1995 May; 73(5):544-50.

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Differential cytokine regulation of PAI-1 gene expression between human umbilical and subcutaneous fat-derived microvascular endothelial cells.
Endothelium. 1995 May; 3:243-52.

Sill HW, Chang YS, Artman JR, Frangos JA, Hollis TM, Tarbell JM.
Shear stress increases hydraulic conductivity of cultured endothelial monolayers.
Am J Physiol. 1995 Feb; 268(2 Pt 2):H535-43.

Thomas GA, Lelkes PI, Chick DM, Lu H, Kowal TA, Hammond RL, Nakajima H, Nakajima H, Spanta AD, Stephenson LW.
Endothelial lined skeletal muscle ventricles: open and percutaneous seeding techniques.
J Card Surg. 1995 May; 10(3):245-56.

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Characterization of skeletal muscle atrophy induced in simulated microgravity culture systems.
Congress on In Vitro Biology.
Denver, CO, USA.May 20-241995.
In Vitro Cell Dev Biol Anim. 1995 Mar;31(3 Pt 2).

Bursac P, Vunjak-Novakovic G, Biron R, Freed LE.
Mass transfer studies of tissue engineered cartilage.
1995 Annual fall meeting of the Biomedical Engineering Society.
Boston, MA, USA.Oct 6-81995.
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Appendix 4 Cells Propagated in the NASA Bioreactor

Propagation of Cells for Tissues

- Cancer models
  - Colon
  - Breast
  - Ovarian
  - Prostate
  - Endocrine
- Normal Tissue
  - Adrenal Medulla
  - Cardiac muscle
  - Cartilage
  - Cornea
  - Liver for hepatitis pathogenicity model
  - Human Kidney
  - Intestinal epithelium for Norwalk virus production for vaccines
  - Liver for extra corporeal support
  - Lymphoid tissue for HIV pathogenesis
  - Neuroendocrine cells
  - Thyroid
  - Skin
  - Pancreatic islet cells
  - Renal Proximal Tubule
  - Tonsil
  - Trachea
  - Umbilical Vein

Tissues from the Bowhead whale

Kidney

Brain

Cell Lines Used

CD34+
506 SM
AcNPV
AGS
BHK
BRS 10
BRS 3
BT-20
C2C12
C3H (H-2k)
C4-2
C57BL10(H-2b)
CHR2A
CHRB
CRL 1502
CX-1
D1
DU-145
EMS-3
HBL 27
HBL-100
HBM 10
HBR 51
HBR 65
HBR 84
HBR 9
HDBR 147
Hep 3B
HepG2
HGF
HL-60
HLB 2
HLT
HMVEC
HOS
HR-1
HRCE
HUC 1
L1210
LN1
LNCaP
LS174T
MC3T3-E1
MCF-7
MDA-MB-231
MG-63
MHC
MIP-101
MOLT-4
NG108-15
NPF 209
O1 T
OT 2
PC-3
PC-12
PDLF
PHH
S2LO-VCAM
SaOS-2
Sf21
Sf-9
SK-HEP1
ST536D
SV-40
SY5Y
T47D
Tn-4h
TN5B 1-4
tsFH1
U2OS
U937
UMR-106

<u>Propagation for Space Cell Biology</u>

- Cellular movement
- Signal transduction across the membrane
- Apoptosis- programmed cell death
- Gene expression
- Immunomodulation
- Recombinant gene products
- In vitro model for renal toxicity
- In vitro analysis of environmental hazards to endangered species
- Angiogenesis- formation of blood vessels
- Virus replication
- Cellular basis of space adaptation phenomena